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(54) Title: COMPOSITIONS ISOLATED FROM SKIN CELLS AND METHODS FOR THEIR USE

(57) Abstract: Isolated polynucleotides encoding polypeptides expressed in mammalian skin cells are provided, together with expression vectors and host cells comprising such isolated polynucleotides. Methods for the use of such polynucleotides and polypeptides are also provided.

# COMPOSITIONS ISOLATED FROM SKIN CELLS AND METHODS FOR THEIR USE

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#### Technical Field of the Invention

This invention relates to polynucleotides, polypeptides, polypeptides expressed in skin cells, and various methods for treating a patient involving administration of a polypeptide or polynucleotide of the present invention.

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#### Background of the Invention

The skin is the largest organ in the body and serves as a protective cover. The loss of skin, as occurs in a badly burned person, may lead to death owing to the absence of a barrier against infection by external microbial organisms, as well as loss of body temperature and body fluids.

Skin tissue is composed of several layers. The outermost layer is the epidermis which is supported by a basement membrane and overlies the dermis. Beneath the dermis is loose connective tissue and fascia which cover muscles or bony tissue. The skin is a self-renewing tissue in that cells are constantly being formed and shed. The deepest cells of the epidermis are the basal cells, which are enriched in cells capable of replication. Such replicating cells are called progenitor or stem cells. Replicating cells in turn give rise to daughter cells called 'transit amplifying cells'. These cells undergo differentiation and maturation into keratinocytes (mature skin cells) as they move from the basal layer to the more superficial layers of the epidermis. In the process, keratinocytes become cornified and are ultimately shed from the skin surface. Other cells in the epidermis include melanocytes which synthesize melanin, the pigment responsible for protection against sunlight. The Langerhans cell also resides in the epidermis and functions as a cell which processes foreign proteins for presentation to the immune system.

The dermis contains nerves, blood and lymphatic vessels, fibrous and fatty tissue. Within the dermis are fibroblasts, macrophages and mast cells. Both the epidermis and dermis are penetrated by sweat, or sebaceous glands and hair follicles. Each strand of hair is derived from a hair follicle. When hair is plucked out, the hair re-grows from epithelial cells directed by the dermal papillae of the hair follicle.

When the skin surface is breached, for example in a wound, the stem cells proliferate and daughter keratinocytes migrate across the wound to reseal the tissues. The skin cells therefore possess genes activated in response to trauma. The products of these genes include several growth factors, such as epidermal growth factor, which mediate the proliferation of skin cells. The genes that are activated in the skin, and the protein products of such genes, may be developed as agents for the treatment of skin wounds. Additional growth factors derived from skin cells may also influence growth of other cell types. As skin cancers are a disorder of the growth of skin cells, proteins derived from skin that regulate cellular growth may be developed as agents for the treatment of skin cancers. Skin derived proteins that regulate the production of melanin may be useful as agents, which protect skin against unwanted effects of sunlight.

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Keratinocytes are known to secrete cytokines and express various cell surface proteins. Cytokines and cell surface molecules are proteins, which play an important role in the inflammatory response against infection, and also in autoimmune diseases affecting the skin. Genes and their protein products that are expressed by skin cells may thus be developed into agents for the treatment of inflammatory disorders affecting the skin.

Hair is an important part of a person's individuality. Disorders of the skin may lead to hair loss. Alopecia areata is a disease characterized by the patchy loss of hair over the scalp. Total baldness is a side effect of drug treatment for cancer. The growth and development of hair is mediated by the effects of genes expressed in skin and dermal papillae. Such genes and their protein products may be usefully developed into agents for the treatment of disorders of the hair follicle.

New treatments are required to hasten the healing of skin wounds, to prevent the loss of hair, enhance the re-growth of hair or removal of hair, and to treat autoimmune

and inflammatory skin diseases more effectively and without adverse effects. More effective treatments of skin cancers are also required. There thus remains a need in the art for the identification and isolation of genes encoding proteins expressed in the skin, for use in the development of therapeutic agents for the treatment of disorders including those associated with skin.

#### Summary of the Invention

The present invention provides polypeptides and functional portions of polypeptides, which may be expressed in skin cells, together with polynucleotides encoding such polypeptides or functional portions thereof, expression vectors and host cells comprising such polynucleotides, and methods for their use.

In specific embodiments, isolated polynucleotides are provided that comprise a polynucleotide selected from the group consisting of: (a) sequences recited in SEQ ID NOS: 1-119, 198-276, 349-372, 399-405, 410-412, 416, 418-455, 464, 466-487, 510, 511 and 514-623; (b) complements of the sequences recited in SEQ ID NOS: 1-119, 198-276, 349-372, 399-405, 410-412, 416, 418-455, 464, 466-487, 510, 511 and 514-623; (c) reverse complements of the sequences recited in SEQ ID NOS: 1-119, 198-276, 349-372, 399-405, 410-412, 416, 418-455, 464, 466-487, 510, 511 and 514-623; (d) reverse sequences of the sequences recited in SEQ ID NOS: 1-119, 198-276, 349-372, 399-405, 410-412, 416, 418-455, 464, 466-487, 510, 511 and 514-623; (e) sequences having a 99% probability of being the same as a sequence of (a)-(d); and (f) sequences having at least 50%, 75%, 90% or 95% identity to a sequence of (a)-(d).

In further embodiments, the present invention provides isolated polypeptides comprising an amino acid sequence selected from the group consisting of: (a) sequences provided in SEQ ID NOS: 120-197, 275-348, 373-398, 406-409, 413-415, 417, 456-463, 465, 488-509, 512, 513 and 624-725; and (b) sequences having at least 50%, 75%, 90% or 95% identity to a sequence provided in SEQ ID NOS: 120-197, 275-348, 373-398, 406-409, 413-415, 417, 456-463, 465, 488-509, 512, 513 and 624-725, together with isolated polynucleotides encoding such polypeptides. Isolated polypeptides which

comprise at least a functional portion of a polypeptide comprising an amino acid sequence selected from the group consisting of: (a) sequences provided in SEQ ID NOS: 120-197, 275-348, 373-398, 406-409, 413-415, 417, 456-463, 465, 488-509, 512, 513 and 624-725; and (b) sequences having 50%, 75% or 90% identity to a sequence of SEQ ID NOS: 120-197, 275-348, 373-398, 406-409, 413-415, 417, 456-463, 465, 488-509, 512, 513 and 624-725, are also provided.

In related embodiments, the present invention provides expression vectors comprising the above polynucleotides, together with host cells transformed with such vectors.

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In a further aspect, the present invention provides a method of stimulating keratinocyte growth and motility, inhibiting the growth of epithelial-derived cancer cells, inhibiting angiogenesis and vascularization of tumors, or modulating the growth of blood vessels in a subject, comprising administering to the subject a composition comprising an isolated polypeptide, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: (a) sequences provided in SEQ ID NOS: 187, 196, 342, 343, 395, 397 and 398; and (b) sequences having at least 50%, 75%, 90% or 95% identity to a sequence provided in SEQ ID NOS: 187, 196, 342, 343, 395, 397 and 398.

Methods for modulating skin inflammation in a subject are also provided, the methods comprising administering to the subject a composition comprising an isolated polypeptide, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: (a) sequences provided in SEQ ID NOS: 338 and 347; and (b) sequences having at least 50%, 75%, 90% or 95% identity to a sequence provided in SEQ ID NOS: 338 and 347. In an additional aspect, the present invention provides methods for stimulating the growth of epithelial cells in a subject. Such methods comprise administering to the subject a composition comprising an isolated polypeptide including an amino acid sequence selected from the group consisting of: (a) sequences provided in SEQ ID NOS: 129 and 348; and (b) sequences having at least 50%, 75%, 90% or 95% identity to a sequence provided in SEQ ID NOS: 129 and 348.

In yet a further aspect, methods for inhibiting the binding of HIV-1 to leukocytes, for the treatment of an inflammatory disease or for the treatment of cancer in a subject are provided, the methods comprising administering to the subject a composition comprising an isolated polypeptide including an amino acid sequence selected from the group consisting of: (a) sequences provided in SEQ ID NOS: 340, 344, 345 and 346; and (b) sequences having at least 50%, 75%, 90% or 95% identity to a sequence provided in SEQ ID NOS: 340, 344, 345 and 346.

As detailed below, the isolated polynucleotides and polypeptides of the present invention may be usefully employed in the preparation of therapeutic agents for the treatment of skin disorders.

The above-mentioned and additional features of the present invention, together with the manner of obtaining them, will be best understood by reference to the following more detailed description. All references disclosed herein are incorporated herein by reference in their entirety as if each was incorporated individually.

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#### Brief Description of the Drawings

Fig. 1 shows the results of a Northern analysis of the distribution of huTR1 mRNA in human tissues. Key: He, Heart; Br, Brain; Pl, Placenta; Lu, Lung; Li, Liver; SM, Skeletal muscle; Ki, Kidney; Sp, Spleen; Th, Thymus; Pr, Prostate; Ov, Ovary.

Fig. 2 shows the results of a MAP kinase assay of muTR1a and huTR1a. MuTR1a (500ng/ml), huTR1a (100ng/ml) or LPS (3pg/ml) were added as described in the text.

Fig. 3 shows the stimulation of growth of neonatal foreskin keratinocytes by muTR1a.

Fig. 4 shows the stimulation of growth of the transformed human keratinocyte cell line HaCaT by muTR1a and huTR1a.

Fig. 5 shows the inhibition of growth of the human epidermal carcinoma cell line A431 by muTR1a and huTR1a.

Fig. 6 shows the inhibition of IL-2 induced growth of concanavalin A-stimulated

murine splenocytes by KS2a.

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Fig. 7 shows the stimulation of growth of rat intestinal epithelial cells (IEC-18) by a combination of KS3a plus apo-transferrin.

Fig. 8 illustrates the oxidative burst effect of TR-1 (100 ng/ml), muKS1 (100 ng/ml), SDF1 $\alpha$  (100 ng/ml), and fMLP (10  $\mu$ M) on human PBMC.

Figure 9 shows the chemotactic effect of muKS1 and SDF-1α on THP-1 cells.

Figure 10 shows the induction of cellular infiltrate in C3H/HeJ mice after intraperitoneal injections with muKS1 (50  $\mu$ g), GV14B (50  $\mu$ g) and PBS.

Figure 11 demonstrates the induction of phosphorylation of ERK1 and ERK2 in CV1/EBNA and HeLa cell lines by huTR1a.

Figure 12 shows the huTR1 mRNA expression in HeLa cells after stimulation by muTR1, huTR1, huTGFα and PBS (100 ng/ml each).

Figure 13 shows activation of the SRE by muTR1a in PC-12 (Fig. 13A) and HaCaT (Fig. 13B) cells.

Figure 14 shows the inhibition of huTR1a mediated growth on HaCaT cells by an antibody to the EGF receptor.

Figure 15A shows the nucleotide sequence of KS1 cDNA (SEQ ID NO: 464) along with the deduced amino acid sequence (SEQ ID NO: 465) using single letter code. The 5' UTR is indicated by negative numbers. The underlined NH<sub>2</sub>-terminal amino acids represent the predicted leader sequence and the stop codon is denoted by \*\*\*. The polyadenylation signal is marked by a double underline. Figure 15B shows a comparison of the complete open reading frame of KS1 (referred to in Fig. 15B as KLF-1) with its human homologue BRAK and with the mouse α-chemokines mCrg-2, mMig, mSDF-1, mBLC, mMIP2, mKC and mLIX. An additional five residues are present in KS1 and BRAK between cysteine 3 and cysteine 4 that have not previously been described for chemokines.

#### Detailed Description of the Invention

In one aspect, the present invention provides polynucleotides that were isolated from mammalian skin cells. As used herein, the term "polynucleotide" means a single or

double-stranded polymer of deoxyribonucleotide or ribonucleotide bases and includes DNA and RNA molecules, both sense and anti-sense strands. The term comprehends cDNA, genomic DNA, recombinant DNA and wholly or partially synthesized nucleic acid molecules. A polynucleotide may consist of an entire gene, or a portion thereof. A gene is a DNA sequence that codes for a functional protein or RNA molecule. Operable anti-sense polynucleotides may comprise a fragment of the corresponding polynucleotide, and the definition of "polynucleotide" therefore includes all operable anti-sense fragments. Anti-sense polynucleotides and techniques involving anti-sense polynucleotides are well known in the art and are described, for example, in Robinson-Benion et al., "Anti-sense Techniques," *Methods in Enzymol.* 254(23):363-375, 1995; and Kawasaki et al., *Artific. Organs* 20(8):836-848, 1996.

Identification of genomic DNA and heterologous species DNAs can be accomplished by standard DNA/DNA hybridization techniques, under appropriately stringent conditions, using all or part of a cDNA sequence as a probe to screen an appropriate library. Alternatively, PCR techniques using oligonucleotide primers that are designed based on known genomic DNA, cDNA and protein sequences can be used to amplify and identify genomic and cDNA sequences. Synthetic DNAs corresponding to the identified sequences and variants may be produced by conventional synthesis methods. All the polynucleotides provided by the present invention are isolated and purified, as those terms are commonly used in the art.

In specific embodiments, the polynucleotides of the present invention comprise a sequence selected from the group consisting of sequences provided in SEQ ID NOS: 1-119, 198-274, 349-372, 399-405, 410-412, 416, 418-455, 464, 466-487, 510, 511 and 514-623, and variants of the sequences of SEQ ID NOS: 1-119, 198-274, 349-372, 399-405, 410-412, 416, 418-455, 464, 466-487, 510, 511 and 514-623. Polynucleotides that comprise complements of such sequences, reverse complements of such sequences, or reverse sequences of such sequences, together with variants of such sequences, are also provided.

The definition of the terms "complement," "reverse complement," and "reverse sequence," as used herein, is best illustrated by the following example. For the sequence 5' AGGACC 3', the complement, reverse complement, and reverse sequence are as follows:

complement 3' TCCTGG 5'
reverse complement 3' GGTCCT 5'
reverse sequence 5' CCAGGA 3'.

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As used herein, the term "complement" refers to sequences that are fully complementary to a sequence disclosed herein.

In another aspect, the present invention provides isolated polypeptides and functional portions of polypeptides encoded, or partially encoded, by the above polynucleotides. As used herein, the term "polypeptide" encompasses amino acid chains of any length, including full length proteins, wherein the amino acid residues are linked by covalent peptide bonds. The term "polypeptide encoded by a polynucleotide" as used herein, includes polypeptides encoded by a polynucleotide which comprises a partial isolated DNA sequence provided herein. In specific embodiments, the inventive polypeptides comprise an amino acid sequence selected from the group consisting of sequences provided in SEQ ID NOS: 120-197, 275-348, 373-398, 406-409, 413-415, 417, 456-463, 465, 488-509, 512, 513 and 624-725, as well as variants of such sequences.

Polypeptides of the present invention may be produced recombinantly by inserting a DNA sequence that encodes the polypeptide into an expression vector and expressing the polypeptide in an appropriate host. Any of a variety of expression vectors known to those of ordinary skill in the art may be employed. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast, and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, insect, yeast, or a mammalian cell line such as COS or CHO. The DNA sequences expressed in this manner may encode naturally occurring polypeptides, portions of naturally occurring polypeptides, or other variants thereof.

In a related aspect, polypeptides are provided that comprise at least a functional portion of a polypeptide having an amino acid sequence selected from the group consisting of sequences provided in SEQ ID NOS: 120-197, 275-348, 373-398, 406-409, 413-415, 417, 456-463, 465, 488-509, 512-513 and 624-725, and variants thereof. As used herein, the "functional portion" of a polypeptide is that portion which contains the active site essential for affecting the function of the polypeptide, for example, the portion of the molecule that is capable of binding one or more reactants. The active site may be made up of separate portions present on one or more polypeptide chains and will generally exhibit high binding affinity.

Functional portions of a polypeptide may be identified by first preparing fragments of the polypeptide by either chemical or enzymatic digestion of the polypeptide, or by mutation analysis of the polynucleotide that encodes the polypeptide and subsequent expression of the resulting mutant polypeptides. The polypeptide fragments or mutant polypeptides are then tested to determine which portions retain biological activity, using, for example, the representative assays provided below.

Portions and other variants of the inventive polypeptides may also be generated by synthetic or recombinant means. Synthetic polypeptides having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may be generated using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See Merrifield, J. Am. Chem. Soc. 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems, Inc. (Foster City, California), and may be operated according to the manufacturer's instructions. Variants of a native polypeptide may be prepared using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis (Kunkel, T., Proc. Natl. Acad. Sci. USA 82:488-492, 1985). Sections of DNA sequence

may also be removed using standard techniques to permit preparation of truncated polypeptides.

In general, the polypeptides disclosed herein are prepared in an isolated, substantially pure, form. Preferably, the polypeptides are at least about 80% pure, more preferably at least about 90% pure, and most preferably at least about 99% pure. In certain preferred embodiments, described in detail below, the isolated polypeptides are incorporated into pharmaceutical compositions or vaccines for use in the treatment of skin disorders.

As used herein, the term "variant" comprehends nucleotide or amino acid sequences different from the specifically identified sequences, wherein one or more nucleotides or amino acid residues is deleted, substituted, or added. Variants may be naturally occurring allelic variants, or non-naturally occurring variants. In certain preferred embodiments, variants of the inventive sequences retain certain, or all, of the functional characteristics of the inventive sequence. Variant sequences (polynucleotide or polypeptide) preferably exhibit at least 50%, more preferably at least 75%, and most preferably at least 90% or 95% identity to a sequence of the present invention. The percentage identity is determined by aligning the two sequences to be compared as described below, determining the number of identical residues in the aligned portion, dividing that number by the total number of residues in the inventive (queried) sequence, and multiplying the result by 100.

Polynucleotide or polypeptide sequences may be aligned, and percentages of identical nucleotides in a specified region may be determined against another polynucleotide or polypeptide, using computer algorithms that are publicly available. Two exemplary algorithms for aligning and identifying the similarity of polynucleotide sequences are the BLASTN and FASTA algorithms. The alignment and similarity of polypeptide sequences may be examined using the BLASTP and algorithm. BLASTX and FASTX algorithms compare nucleotide query sequences translated in all reading frames against polypeptide sequences. The BLASTN, BLASTP and BLASTX algorithms are available on the NCBI anonymous FTP server (ftp://ncbi.nlm.nih.gov)

under /blast/executables/ and are available from the National Center for Biotechnology Information (NCBI), National Library of Medicine, Building 38A, Room 8N805, Bethesda, MD 20894 USA.

The FASTA and FASTX algorithms are available on the Internet at the ftp site ftp://ftp.Virginia.edu/pub/. The FASTA software package is also available from the University of Virginia by contacting David Hudson, Assistant Provost for Research, University of Virginia, PO Box 9025, Charlottesville, VA 22906-9025. The FASTA algorithm, set to the default parameters described in the documentation and distributed with the algorithm, may be used in the determination of polynucleotide variants. The readme files for FASTA and FASTX v1.0x that are distributed with the algorithms describe the use of the algorithms and describe the default parameters. The use of the FASTA and FASTX algorithms is also described in Pearson, and Lipman, *Proc. Natl. Acad. Sci. USA* 85:2444-2448, 1988; and Pearson, *Methods in Enzymol.* 183:63-98, 1990.

The BLASTN algorithm version 2.0.4 [Feb-24-1998], 2.0.6 [Sept-16-1998] and 2.0.11 [Jan-20-2000], set to the default parameters described in the documentation and distributed with the algorithm, is preferred for use in the determination of polynucleotide variants according to the present invention. The BLASTP algorithm version 2.0.4, 2.0.6 and 2.0.11, set to the default parameters described in the documentation and distributed with the algorithm, is preferred for use in the determination of polypeptide variants according to the present invention. The use of the BLAST family of algorithms, including BLASTN, BLASTP and BLASTX is described in the publication of Altschul, et al., Nucleic Acids Res. 25:3389-3402, 1997.

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The following running parameters are preferred for determination of alignments and similarities using BLASTN that contribute to the E values and percentage identity for polynucleotides: Unix running command with default parameters thus: blastall -p blastn - d embldb -e 10 -G 0 -E 0 -r 1 -v 30 -b 30 -i queryseq -o results; and parameters are: -p Program Name [String]; -d Database [String]; -e Expectation value (E) [Real]; -G Cost to open a gap (zero invokes default behavior) [Integer]; -E Cost to extend a gap (zero

invokes default behavior) [Integer]; -r Reward for a nucleotide match (blastn only) [Integer]; -v Number of one-line descriptions (V) [Integer]; -b Number of alignments to show (B) [Integer]; -i Query File [File In]; -o BLAST report Output File [File Out] Optional. The following running parameters are preferred for determination of alignments and similarities using BLASTP that contribute to the E values and percentage identity for polypeptides: blastall -p blastp -d swissprotdb -e 10 -G 1 -E 11 -r 1 -v 30 -b 30 -i queryseq -o results; and the parameters are: -p Program Name [String]; -d Database [String]; -e Expectation value (E) [Real]; -G Cost to open a gap (zero invokes default behavior) [Integer]; -E Cost to extend a gap (zero invokes default behavior) [Integer]; -v Number of one-line descriptions (v) [Integer]; -b Number of alignments to show (b) [Integer]; -I Query File [File In]; -o BLAST report Output File [File Out] Optional.

The "hits" to one or more database sequences by a queried sequence produced by BLASTN, BLASTP, FASTA, or a similar algorithm, align and identify similar portions of sequences. The hits are arranged in order of the degree of similarity and the length of sequence overlap. Hits to a database sequence generally represent an overlap over only a fraction of the sequence length of the queried sequence.

As noted above, the percentage identity of a polynucleotide or polypeptide sequence is determined by aligning polynucleotide and polypeptide sequences using appropriate algorithms, such as BLASTN or BLASTP, respectively, set to default parameters; identifying the number of identical nucleic or amino acids over the aligned portions; dividing the number of identical nucleic or amino acids by the total number of nucleic or amino acids of the polynucleotide or polypeptide of the present invention; and then multiplying by 100 to determine the percentage identity. By way of example, a queried polynucleotide having 220 nucleic acids has a hit to a polynucleotide sequence in the EMBL database having 520 nucleic acids over a stretch of 23 nucleotides in the alignment produced by the BLASTN algorithm using the default parameters. The 23 nucleotide hit includes 21 identical nucleotides, one gap and one different nucleotide. The percentage identity of the queried polynucleotide to the hit in the EMBL database is

thus 21/220 times 100, or 9.5%. The identity of polypeptide sequences may be determined in a similar fashion.

The BLASTN and BLASTX algorithms also produce "Expect" values for polynucleotide and polypeptide alignments. The Expect value (E) indicates the number of hits one can "expect" to see over a certain number of contiguous sequences by chance when searching a database of a certain size. The Expect value is used as a significance threshold for determining whether the hit to a database indicates true similarity. For example, an E value of 0.1 assigned to a polynucleotide hit is interpreted as meaning that in a database of the size of the EMBL database, one might expect to see 0.1 matches over the aligned portion of the sequence with a similar score simply by chance. By this criterion, the aligned and matched portions of the sequences then have a probability of 90% of being the same. For sequences having an E value of 0.01 or less over aligned and matched portions, the probability of finding a match by chance in the EMBL database is 1% or less using the BLASTN algorithm. E values for polypeptide sequences may be determined in a similar fashion using various polypeptide databases, such as the SwissProt database.

According to one embodiment, "variant" polynucleotides and polypeptides, with reference to each of the polynucleotides and polypeptides of the present invention, preferably comprise sequences having the same number or fewer nucleic or amino acids than each of the polynucleotides or polypeptides of the present invention and producing an E value of 0.01 or less when compared to the polynucleotide or polypeptide of the present invention. That is, a variant polynucleotide or polypeptide is any sequence that has at least a 99% probability of being the same as the polynucleotide or polypeptide of the present invention, measured as having an E value of 0.01 or less using the BLASTN or BLASTX algorithms set at the default parameters. According to a preferred embodiment, a variant polynucleotide is a sequence having the same number or fewer nucleic acids than a polynucleotide of the present invention that has at least a 99% probability of being the same as the polynucleotide of the present invention, measured as having an E value of 0.01 or less using the BLASTN algorithm set at the default

parameters. Similarly, according to a preferred embodiment, a variant polypeptide is a sequence having the same number or fewer amino acids than a polypeptide of the present invention that has at least a 99% probability of being the same as the polypeptide of the present invention, measured as having an E value of 0.01 or less using the BLASTP algorithm set at the default parameters.

Variant polynucleotide sequences will generally hybridize to the recited polynucleotide sequences under stringent conditions. As used herein, "stringent conditions" refers to prewashing in a solution of 6X SSC, 0.2% SDS; hybridizing at 65°C, 6X SSC, 0.2% SDS overnight; followed by two washes of 30 minutes each in 1X SSC, 0.1% SDS at 65 °C and two washes of 30 minutes each in 0.2X SSC, 0.1% SDS at 65 °C.

As used herein, the term "x-mer," with reference to a specific value of "x," refers to a polynucleotide or polypeptide, respectively, comprising at least a specified number ("x") of contiguous residues of: any of the polynucleotides provided in SEQ ID NO: 1-119, 198-274, 349-372, 399-405, 410-412, 416, 418-455, 464, 466-487, 510, 511 and 514-623; or any of the polypeptides set out in SEQ ID NO: 120-197, 275-348, 373-398, 406-409, 413-415, 417, 456-463, 465, 488-509, 512, 513 and 624-725. The value of x may be from about 20 to about 600, depending upon the specific sequence.

Polynucleotides of the present invention comprehend polynucleotides comprising at least a specified number of contiguous residues (x-mers) of any of the polynucleotides identified as SEQ ID NO: 1-119, 198-274, 349-372, 399-405, 410-412, 416, 418-455, 464, 466-487, 510, 511 and 514-623, or their variants. Polypeptides of the present invention comprehend polypeptides comprising at least a specified number of contiguous residues (x-mers) of any of the polypeptides identified as SEQ ID NO: 120-197, 275-348, 373-398, 406-409, 413-415, 417, 456-463, 465, 488-509, 512, 513 and 624-725. According to preferred embodiments, the value of x is at least 20, more preferably at least 40, more preferably yet at least 60, and most preferably at least 80. Thus, polynucleotides of the present invention include polynucleotides comprising a 20-mer, a 40-mer, a 60-mer, an 80-mer, a 100-mer, a 120-mer, a 150-mer, a 180-mer, a 220-mer, a

250-mer; or a 300-mer, 400-mer, 500-mer or 600-mer of a polynucleotide provided in SEQ ID NOS: 1-119, 198-274, 349-372, 399-405, 410-412, 416, 418-455, 464, 466-487, 510, 511 and 514-623, or of a variant of one of the polynucleotides provided in SEQ ID NO: 1-119, 198-274, 349-372, 399-405, 410-412, 416, 418-455, 464, 466-487, 510, 511 and 514-623. Polypeptides of the present invention include polypeptides comprising a 20-mer, a 40-mer, a 60-mer, an 80-mer, a 100-mer, a 120-mer, a 150-mer, a 180-mer, a 220-mer, a 250-mer; or a 300-mer, 400-mer, 500-mer or 600-mer of a polypeptide provided in SEQ ID NOS: 120-197, 275-348, 373-398, 406-409, 413-415, 417, 456-463, 465, 488-509, 512, 513 and 624-725, or of a variant of one of the polypeptides provided in SEQ ID NOS: 120-197, 275-348, 373-398, 406-409, 413-415, 417, 456-463, 465, 488-509, 512, 513 and 624-725.

The inventive polynucleotides may be isolated by high throughput sequencing of cDNA libraries prepared from mammalian skin cells as described below in Example 1. Alternatively, oligonucleotide probes based on the sequences provided in SEQ ID NOS: 1-119, 198-274, 349-372, 399-405, 410-412, 416, 418-455, 464, 466-487, 510, 511 and 514-623 can be synthesized and used to identify positive clones in either cDNA or genomic DNA libraries from mammalian skin cells by means of hybridization or polymerase chain reaction (PCR) techniques. Probes can be shorter than the sequences provided herein but should be at least about 10, preferably at least about 15 and most preferably at least about 20 nucleotides in length. Hybridization and PCR techniques suitable for use with such oligonucleotide probes are well known in the art (see, for example, Mullis, et al., Cold Spring Harbor Symp. Quant. Biol., 51:263, 1987; Erlich, ed., PCR Technology, Stockton Press: NY, 1989; (Sambrook, J, Fritsch, EF and Maniatis, T, eds., Molecular Cloning: A Laboratory Manual, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor: New York, 1989). Positive clones may be analyzed by restriction enzyme digestion, DNA sequencing or the like.

In addition, DNA sequences of the present invention may be generated by synthetic means using techniques well known in the art. Equipment for automated synthesis of oligonucleotides is commercially available from suppliers such as Perkin

Elmer/Applied Biosystems Division (Foster City, California) and may be operated according to the manufacturer's instructions.

Since the polynucleotide sequences of the present invention have been derived from skin, they likely encode proteins that have important roles in growth and development of skin, and in responses of skin to tissue injury and inflammation as well as disease states. Some of the polynucleotides contain sequences that code for signal sequences, or transmembrane domains, which identify the protein products as secreted molecules or receptors. Such protein products are likely to be growth factors, cytokines, or their cognate receptors. Several of the polypeptide sequences have more than 25% similarity to known biologically important proteins and thus are likely to represent proteins having similar biological functions.

In particular, the inventive polypeptides have important roles in processes such as: induction of hair growth; differentiation of skin stem cells into specialized cell types; cell migration; cell proliferation and cell-cell interaction. The polypeptides are important in the maintenance of tissue integrity, and thus are important in processes such as wound healing. Some of the disclosed polypeptides act as modulators of immune responses, especially since immune cells are known to infiltrate skin during tissue insult causing growth and differentiation of skin cells. In addition, many polypeptides are immunologically active, making them important therapeutic targets in a whole range of disease states not only within skin, but also in other tissues of the body. Antibodies to the polypeptides of the present invention and small molecule inhibitors related to the polypeptides of the present invention may also be used for modulating immune responses and for treatment of diseases according to the present invention.

In one aspect, the present invention provides methods for using one or more of the inventive polypeptides or polynucleotides to treat disorders in a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human.

In this aspect, the polypeptide or polynucleotide is generally present within a pharmaceutical or immunogenic composition. Pharmaceutical compositions may comprise one or more polypeptides, each of which may contain one or more of the above

sequences (or variants thereof), and a physiologically acceptable carrier. Immunogenic compositions may comprise one or more of the above polypeptides and a non-specific immune response amplifier, such as an adjuvant or a liposome, into which the polypeptide is incorporated.

Alternatively, a pharmaceutical or immunogenic composition of the present invention may contain DNA encoding one or more polypeptides as described above, such that the polypeptide is generated in situ. In such compositions, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, and bacterial and viral expression systems. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminator signal). Bacterial delivery systems involve the administration of a bacterium (such as Bacillus-Calmette-Guerin) that expresses an immunogenic portion of the polypeptide on its cell surface. In a preferred embodiment, the DNA may be introduced using a viral expression system (e.g., vaccinia or other poxvirus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic, or defective, replication competent virus. incorporating DNA into such expression systems are well known in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., Science 259:1745-1749, 1993 and reviewed by Cohen, Science 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

Routes and frequency of administration, as well as dosage, vary from individual to individual. In general, the pharmaceutical and immunogenic compositions may be administered by injection (e.g., intradermal, intramuscular, intravenous, or subcutaneous), intranasally (e.g., by aspiration) or orally. In general, the amount of polypeptide present in a dose (or produced *in situ* by the DNA in a dose) ranges from about 1 pg to about 100 mg per kg of host, typically from about 10 pg to about 1 mg per kg of host, and preferably from about 100 pg to about 1  $\mu$ g per kg of host. Suitable dose

sizes will vary with the size of the patient, but will typically range from about 0.1 ml to about 5 ml.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a lipid, a wax, or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (e.g., polylactic galactide) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.

Any of a variety of adjuvants may be employed in the immunogenic compositions of the invention to non-specifically enhance the immune response. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a non-specific stimulator of immune responses, such as lipid A, Bordetella pertussis, or Mycobacterium tuberculosis. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Freund's Complete Adjuvant (Difco Laboratories, Detroit, Michigan), and Merck Adjuvant 65 (Merck and Company, Inc., Rahway, New Jersey). Other suitable adjuvants include alum, biodegradable microspheres, monophosphoryl lipid A, and Quil A.

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The polynucleotides of the present invention may also be used as markers for tissue, as chromosome markers or tags, in the identification of genetic disorders, and for the design of oligonucleotides for examination of expression patterns using techniques well known in the art, such as the microarray technology available from Affymetrix (Santa Clara, CA). Partial polynucleotide sequences disclosed herein may be employed to obtain full length genes by, for example, screening of DNA expression libraries using hybridization probes or PCR primers based on the inventive sequences.

The polypeptides provided by the present invention may additionally be used in assays to determine biological activity, to raise antibodies, to isolate corresponding ligands or receptors, in assays to quantitatively determine levels of protein or cognate corresponding ligand or receptor, as anti-inflammatory agents, and in compositions for skin, connective tissue and/or nerve tissue growth or regeneration. The present invention further provides methods for modulating expression of the inventive polypeptides, for example by inhibiting translation of the relevant polynucleotide. Translation of the relevant polynucleotide may be inhibited, for example, by introducing anti-sense expression vectors; by introducing antisense oligodeoxyribonucleotides or antisense phosphorothioate oligodeoxyribonucleotides; by introducing antisense oligoribonucleotides or antisense phosphorothioate oligoribonucleotides; or by other means which are well known in the art. Cell permeation and activity of antisense oligonucleotides can be enhanced by appropriate chemical modifications, such as the use of phenoxazine-substituted C-5 propynyl uracil oligonucleotides (Flanagan et al., (1999) Nat. Biotechnol. 17 (1): 48-52) or 2'-O-(2-methoxy) ethyl (2'-MOE)-oligonucleotides (Zhang et al., (2000) Nat. Biotechnol. 18: 862-867). The use of techniques involving antisense polynucleotides is well known in the art and is described, for example, in Robinson-Benion et al. (1995), Antisense techniques, Methods in Enzymol. 254 (23): 363-375 and Kawasaki et al. (1996), Artific. Organs 20 (8): 836-848.

The following Examples are offered by way of illustration and not by way of limitation.

# Example 1 ISOLATION OF CDNA SEQUENCES FROM SKIN CELL EXPRESSION LIBRARIES

The cDNA sequences of the present invention were obtained by high-throughput sequencing of cDNA expression libraries constructed from specialized rodent or human skin cells as shown in Table 1.

Table 1

	Table 1		
	Library	Skin cell type	Source
30	DEPA	dermal papilla	rat

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SKTC	keratinocytes	human
HNFF	neonatal foreskin fibroblast	human
MEMS	embryonic skin	mouse
KSČL	keratinocyte stem cell	mouse
TRAM	transit amplifying cells	mouse
MFSE	epidermis	mouse
HLEA	small epithelial airway cells	human
HLEB	small epithelial airway cells	human
HNKA	NK cells	human

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These cDNA libraries were prepared as described below.

#### cDNA Library from Dermal Papilla (DEPA)

Dermal papilla cells from rat hair vibrissae (whiskers) were grown in culture and the total RNA extracted from these cells using established protocols. Total RNA, isolated using TRIzol Reagent (BRL Life Technologies, Gaithersburg, Maryland), was used to obtain mRNA using a Poly(A) Quik mRNA isolation kit (Stratagene, La Jolla, California), according to the manufacturer's specifications. A cDNA expression library was then prepared from the mRNA by reverse transcriptase synthesis using a Lambda ZAP cDNA library synthesis kit (Stratagene).

#### cDNA Library from Keratinocytes (SKTC)

Keratinocytes obtained from human neonatal foreskins (Mitra, R and Nikoloff, B in *Handbook of Keratinocyte Methods*, pp. 17-24, 1994) were grown in serum-free KSFM (BRL Life Technologies) and harvested along with differentiated cells (10<sup>8</sup> cells). Keratinocytes were allowed to differentiate by addition of fetal calf serum at a final concentration of 10% to the culture medium and cells were harvested after 48 hours. Total RNA was isolated from the two cell populations using TRIzol Reagent (BRL Life Technologies) and used to obtain mRNA using a Poly(A) Quik mRNA isolation kit

(Stratagene). cDNAs expressed in differentiated keratinocytes were enriched by using a PCR-Select cDNA Subtraction Kit (Clontech, Palo Alto, California). Briefly, mRNA was obtained from either undifferentiated keratinocytes ("driver mRNA") or differentiated keratinocytes ("tester mRNA") and used to synthesize cDNA. The two populations of cDNA were separately digested with RsaI to obtain shorter, blunt-ended molecules. Two tester populations were created by ligating different adaptors at the cDNA ends and two successive rounds of hybridization were performed with an excess of driver cDNA. The adaptors allowed for PCR amplification of only the differentially expressed sequences which were then ligated into T-tailed pBluescript (Hadjeb, N and Berkowitz, GA, BioTechniques 20:20-22 1996), allowing for a blue/white selection of cells containing vector with inserts. White cells were isolated and used to obtain plasmid DNA for sequencing.

#### cDNA library from human neonatal fibroblasts (HNFF)

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Human neonatal fibroblast cells were grown in culture from explants of human neonatal foreskin and the total RNA extracted from these cells using established protocols. Total RNA, isolated using TRIzol Reagent (BRL Life Technologies, Gaithersburg, Maryland), was used to obtain mRNA using a Poly(A) Quik mRNA isolation kit (Stratagene, La Jolla, California), according to the manufacturer's specifications. A cDNA expression library was then prepared from the mRNA by reverse transcriptase synthesis using a Lambda ZAP cDNA library synthesis kit (Stratagene).

#### cDNA library from mouse embryonic skin (MEMS)

Embryonic skin was micro-dissected from day 13 post coitum Balb/c mice. Embryonic skin was washed in phosphate buffered saline and mRNA directly isolated from the tissue using the Quick Prep Micro mRNA purification kit (Pharmacia, Sweden). The mRNA was then used to prepare cDNA libraries as described above for the DEPA library.

0 <u>cDNA library from mouse stem cells (KSCL) and transit amplifying (TRAM) cells</u>

Pelts obtained from 1-2 day post-partum neonatal Balb/c mice were washed and incubated in trypsin (BRL Life Technologies) to separate the epidermis from the dermis. Epidermal tissue was disrupted to disperse cells, which were then resuspended in growth medium and centrifuged over Percoll density gradients prepared according to the manufacturer's protocol (Pharmacia, Sweden). Pelleted cells were labeled using Rhodamine 123 (Bertoncello I, Hodgson GS and Bradley TR, Exp Hematol. 13:999-1006, 1985), and analyzed by flow cytometry (Epics Elite Coulter Cytometry, Hialeah, Florida). Single cell suspensions of rhodamine-labeled murine keratinocytes were then labeled with a cross reactive anti-rat CD29 biotin monoclonal antibody (Pharmingen, San Diego, California; clone Ha2/5). Cells were washed and incubated with anti-mouse CD45 phycoerythrin conjugated monoclonal antibody (Pharmingen; clone 30F11.1, 10ug/ml) followed by labeling with streptavidin spectral red (Southern Biotechnology, Birmingham, Alabama). Sort gates were defined using listmode data to identify four populations: CD29 bright rhodamine dull CD45 negative cells; CD29 bright rhodamine bright CD45 negative cells; CD29 dull rhodamine bright CD45 negative cells; and CD29 dull rhodamine dull CD45 negative cells. Cells were sorted, pelleted and snap frozen prior to storage at -80°C. This protocol was followed multiple times to obtain sufficient cell numbers of each population to prepare cDNA libraries. Skin stem cells and transit amplifying cells are known to express CD29, the integrin \$1 chain. CD45, a leukocyte specific antigen, was used as a marker for cells to be excluded in the isolation of skin stem cells and transit amplifying cells. Keratinocyte stem cells expel the rhodamine dye more efficiently than transit amplifying cells. The CD29 bright, rhodamine dull, CD45 negative population (putative keratinocyte stem cells; referred to as KSCL), and the CD29 bright, rhodamine bright, CD45 negative population (keratinocyte transit amplifying cells; referred to as TRAM) were sorted and mRNA was directly isolated from each cell population using the Quick Prep Micro mRNA purification kit (Pharmacia, Sweden). The mRNA was then used to prepare cDNA libraries as described above for the DEPA library.

#### cDNA Library from Epithelial Cells (MFSE)

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Skin epidermis was removed from flaky skin fsn -/- mice (The Jackson Laboratory, Bar Harbour, ME), the cells dissociated and the resulting single cell suspension placed in culture. After four passages, the cells were harvested. Total RNA, isolated using TRIzol Reagent (BRL Life Technologies, Gaithersburg, MD), was used to obtain mRNA using a Poly(A)Quik mRNA isolation kit (Stratagene, La Jolla, CA), according to the manufacturer's specifications. A cDNA expression library (referred to as the MFSE library) was then prepared from the mRNA by Reverse Transcriptase synthesis using a Lambda ZAP Express cDNA library synthesis kit (Stratagene, La Jolla, CA).

#### cDNA Libraries from Human Small Airway Epithelial Cells (HLEA and HLEB)

Human small airway epithelium cells SAEC (Cell line number CC-2547, Clonetics Normal Human Cell Systems, Cambrex Corporation, East Rutherford NJ) transformed with human papilloma virus E6E7 that was infected with the bacterium  $Yersinia\ enterocolitica\ (ATCC\ No.\ 51871,\ American\ Type\ Culture\ Collection,\ Manassas\ VA)$  and the long form of the Respiratory Syncytial Virus (RSV, ATCC No. VR26), were used as source of RNA to construct the libraries called HLEA and HLEB. Cells from the twelfth passage of SAEC cells were infected with Y. enterocolitica for 2 hours at an initial seed of 12.5 bacteria per cell. The cells were disinfected with gentamycin (100  $\mu$ g/ml) for 2 hours and harvested 4 hours after infection. The cells were then infected with RSV at a moiety of infection of 0.7 for 1 hour and incubated for 6 and 24 hours. Cells were harvested and the RNA extracted following standard protocols.

Total RNA, isolated using TRIzol Reagent (BRL Life Technologies, Gaithersburg, Maryland), was used to obtain mRNA using a Poly(A) Quik mRNA isolation kit (Stratagene, La Jolla, CA), according to the manufacturer's specifications. Two cDNA expression libraries were then prepared from the mRNA by reverse transcriptase synthesis using a Lambda ZAP cDNA library synthesis kit (Stratagene).

cDNA Library from Epithelial Cells (HNKA)

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The subtracted cDNA library (HNKA) from human natural killer (NK) cells was constructed as follows. A NK library was first constructed using pooled RNA extracted from primary NK cells from multiple donors, stimulated for 4 or 20 hours with IL-2 (10 ng/ml), IL-12 (1 ng/ml), IL-15 (50 ng/ml), interferon alpha (IFN-α; 1,000 U/ml) immobilized anti-CD16 or immobilized anti-NAIL antibody, or from unstimulated cells. RNA was extracted following standard procedures. cDNA was prepared using a TimeSaver kit (Pharmacia, Uppsala, Sweden) following the manufacturer's protocol. The cDNA was ligated to *Bgl*II adaptors and size-selected using cDNA sizing columns (Gibco BRL, Gaithersburg MD). The size-selected NK cDNA was ligated into a pDc 409 vector and transformed into *E. coli* DH105 cells. Single-stranded DNA was prepared from the plasmid library using a helper phage (Stratagene)

A second cDNA library (referred to as FF cDNA library) was constructed using fetal foreskin tissue. RNA was extracted and cDNA prepared following standard protocols. The cDNA was ligated into the plasmid pBluescript following standard protocols. 10  $\mu$ g of the FF cDNA library was linearized with the restriction endonuclease *Not*I and used as template to synthesize biotin-labeled cRNA using SP6 polymerase.

The subtracted NK cell library (HNKA) was constructed as follows. The biotinylated FF cRNA was mixed with the NK library, ethanol precipitated and resuspended in  $5\,\mu$ l buffer (50 mM HEPES pH 7.4, 10 mM EDTA, 1.5 M NaCl, 0.2% SDS). After addition of  $5\,\mu$ l formamide and heating to 95° for 1 min, the material was left to hybridize for 24 hours at 42°C. 90  $\mu$ l of 10 mM HEPES pH 7.3, 1 mM EDTA and 15  $\mu$ l streptavidin was added followed by an incubation for 20 min at 50°C. This step was repeated again after extraction with phenol/chloroform.

To the final extracted aqueous phase, the following were added: NaCl to 0.2 M, 1  $\mu$ l glycogen and 2 volumes of ethanol. After an overnight precipitation at -20°C, the DNA was pelleted and resuspended in 10  $\mu$ l water. A second round of subtraction was performed as above and the DNA transformed into *E. coli* DH105.

cDNA sequences were obtained by high-throughput sequencing of the cDNA libraries described above using a Perkin Elmer/Applied Biosystems Division Prism 377 sequencer.

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#### Example 2

#### CHARACTERIZATION OF ISOLATED CDNA SEQUENCES

The isolated cDNA sequences were compared to sequences in the EMBL DNA database using the computer algorithms FASTA and/or BLASTN. The corresponding protein sequences (DNA translated to protein in each of 6 reading frames) were compared to sequences in the SwissProt database using the computer algorithms FASTX and/or BLASTX. Comparisons of DNA sequences provided in SEQ ID NO: 1-119 to sequences in the EMBL DNA database (using FASTA) and amino acid sequences provided in SEQ ID NO: 120-197 to sequences in the SwissProt database (using FASTX) were made as of March 21, 1998. Comparisons of DNA sequences provided in SEQ ID NO: 198-274 to sequences in the EMBL DNA database (using BLASTN) and amino acid sequences provided in SEQ ID NO: 275-348 to sequences in the SwissProt database (using BLASTP) were made as of October 7, 1998. Comparisons of DNA sequences provided in SEQ ID NO: 349-372 to sequences in the EMBL DNA database (using BLASTN) and amino acid sequences provided in SEQ ID NO: 373-398 to sequences in the SwissProt database (using BLASTP) were made as of January 23, 1999. Comparisons of polynucleotide sequences provided in SEQ ID NO: 418-455 and 466-487 to sequences in the EMBL DNA database (using BLASTN) and polypeptide sequences provided in SEO ID NO: 456-463 and 488-509 to sequences in the SwissProt database (using BLASTP) were made as of April 23, 2000. Comparisons of polynucleotide sequences provided in SEO ID NO: 510 and 511 to sequences in the EMBL DNA database (using BLASTN) and polypeptide sequences provided in SEQ ID NO: 512 and 513 to sequences in the SwissProt database (using BLASTP) were made as of July 11, 2000. Comparisons of polynucleotide sequences provided in SEQ ID NO: 514-623 to

sequences in the EMBL66 - HTGs + ENSEMBL (May 1, 2001) DNA database (using BLASTN) and polypeptide sequences provided in SEQ ID NO: 624-725 to sequences in the SP\_TR\_NRDB + ENSEMBL (April 30, 2001) database (using BLASTP) were made as of May 16, 2001.

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Isolated cDNA sequences and their corresponding polypeptide sequences were computer analyzed for the presence of signal sequences identifying secreted molecules. Isolated cDNA sequences that have a signal sequence at a putative start site within the sequence are provided in SEQ ID NO: 1-44, 198-238, 349-358, 399, 418-434, 440-449 and 466-471, 516, 519, 520, 523-527, 531, 532, 535-537, 548, 555, 574-580, 585-587, 589, 593, 595, 596, 598-601, 605-607, 609, 612, 613, 615, 616 and 622. The cDNA sequences of SEQ ID NO: 1-6, 198-199, 349-352, 354, 356-358,419-428, 430-433, 440-444, 446-448, 466, 468-470, 519, 520, 523, 524, 529, 531, 532, 535-537, 579, 585, 587, 598, 605, 609, 613 and 622 were determined to have less than 75% identity (determined as described above), to sequences in the EMBL database using the computer algorithms FASTA or BLASTN, as described above. The polypeptide sequences of SEQ ID NO: 120-125, 275-276, 373-380, 382, 456, 457, 460-462, 488-493, 633, 637, 642, 683, 685, 691, 693, 703, 706, 710, 714, 717, 718, 720, 721 and 725 were determined to have less than 75% identity (determined as described above) to sequences in the SwissProt database using the computer algorithms FASTX or BLASTP, as described above.

Further sequencing of some of the isolated partial cDNA sequences resulted in the isolation of the full-length cDNA sequences provided in SEQ ID NOS: 7-14, 200-231, 372, 418-422, 441-448, 514, 516, 557-561, 567, 568, 619 and 621. The polypeptide sequences encoded by the cDNA sequences of SEQ ID NO: 7-14, 200-231, 372, 514, 516, 557-561, 567, 568, 619 and 621 are provided in SEQ ID NOS: 126-133, 277-308, 396,624, 626, 666-669, 674 and 724 respectively. The cDNA sequences of SEQ ID NO: 418-422 encode the same amino acid sequences as the cDNA sequences of SEQ ID NO: 7 and 11-14, namely SEQ ID NO: 126 and 130-133, respectively. Comparison of the full-

length cDNA sequences with those in the EMBL database using the computer algorithm FASTA or BLASTN, as described above, revealed less than 75% identity (determined as described above) to known sequences, except for the polynucleotides in SEQ ID NOS: 516, 560 and 619. Comparison of the amino acid sequences provided in SEQ ID NOS: 126-133, 277-308, 666, 668, 669 and 724 with those in the SwissProt database using the computer algorithms FASTX or BLASTP, as described above, revealed less than 75% identity (determined as described above) to known sequences.

Comparison of the polypeptide sequences corresponding to the cDNA sequences of SEQ ID NOS: 15-23 with those in the EMBL database using the computer algorithm FASTA database showed less than 75% identity (determined as described above) to known sequences. These polypeptide sequences are provided in SEO ID NOS: 134-142.

Further sequencing of some of the isolated partial cDNA sequences resulted in the isolation of full-length cDNA sequences provided in SEQ ID NOS: 24-44, 232-238, 423-434, 449, 466, 468-470, 475, 476 and 484. The polypeptide sequences encoded by the cDNA sequences of SEQ ID NO: 24-44, 232-238, 429, 466, 468-470, 475, 476 and 484 are provided in SEQ ID NOS: 143-163, 309-315, 456, 488, 490-492, 497, 498 and 506, respectively. The cDNA sequences of SEQ ID NO: 423-428, 430-434 and 449 encode the same polypeptide sequences as the cDNA sequences of SEQ ID NO: 27-29, 34, 35, 37, 40-44 and 238, namely SEQ ID NO: 146-148, 153, 154, 156, 159-163 and 315, respectively. These polypeptide sequences were determined to have less than 75% identity, determined as described above to known sequences in the SwissProt database using the computer algorithm FASTX.

Isolated cDNA sequences having less than 75% identity to known expressed sequence tags (ESTs) or to other DNA sequences in the public database, or whose corresponding polypeptide sequence showed less than 75% identity to known protein sequences, were computer analyzed for the presence of transmembrane domains coding for putative membrane-bound molecules. Isolated cDNA sequences that have one or more transmembrane domain(s) within the sequence are provided in SEQ ID NOS: 45-63, 239-253, 359-364, 400-402, 435, 436, 450-452, 455, 470-472, 542, 553-555, 573,

576, 581, 592, 593, 595 and 606. The cDNA sequences of SEQ ID NOS: 45-48, 239-249, 359-361, 363, 450, 451, 455, 472, 473, 553-555, 573, 576 and 592 were found to have less than 75% identity (determined as described above) to sequences in the EMBL database, using the FASTA or BLASTN computer algorithms. The polypeptide sequences encoded by the cDNA sequences of SEQ ID NO: 45-48, 239-249, 359-361, 363, 450, 451, 472, 473, 553-555, 573 and 606 (provided in SEQ ID NOS: 164-167, 316-326, 383, 385-388, 407-408, 460, 461, 494, 495, 662, 663, 664, 679, 682 and 711 respectively) were found to have less than 75% identity, determined as described above, to sequences in the SwissProt database using the FASTX or BLASTP database. The cDNA sequence of SEQ ID NO: 455 encodes the same polypeptide sequence as the cDNA sequence of SEQ ID NO: 359, namely SEQ ID NO: 383.

Comparison of the polypeptide sequences corresponding to the cDNA sequences of SEQ ID NOS: 49-63, 250-253, 436 and 452 with those in the SwissProt database showed less than 75% identity (determined as described above) to known sequences. These polypeptide sequences are provided in SEQ ID NOS: 168-182, 327-330, 457 and 462, respectively.

Using automated search programs to screen against sequences coding for molecules reported to be of therapeutic and/or diagnostic use, some of the cDNA sequences isolated as described above in Example 1 were determined to encode polypeptides that are family members of known protein families. A family member is here defined to have at least 25% identity in the translated polypeptide to a known protein or member of a protein family. These cDNA sequences are provided in SEQ ID NOS: 64-76, 254-264, 365-369, 403, 437-439, 453, 454, 475-487, 510, 511, 514-527, 529-531, 533-536, 538-546, 548, 549, 553-559, 562, 564, 565, 567, 569-575, 577-589, 591-602, 604-612, 616-618, 621 and 622. The polypeptide sequences encoded by the cDNA sequences of SEQ ID NO: 64-76, 254-264, 365-369, 403, 438, 439, 453, 475-487, 510 and 511, 514-527, 529-531, 533-536, 538-546, 548, 549, 553-559, 562, 564, 565, 567, 569-575, 577-589, 591-602, 604-612, 616-618, 621 and 622 are provided in SEQ ID NOS: 183-195, 331-341, 389-393, 409, 458, 459, 463, 497-509, 624-637, 639-641, 643-

646, 648-656, 658, 659, 662-668, 670, 672-681, 683-707, 709-717 and 721-725, respectively. The cDNA sequences of SEQ ID NO: 437 and 454 encode the same amino acid sequences as the cDNA sequences of SEQ ID NO: 68 and 262, namely SEQ ID NO: 187 and 339, respectively. The cDNA sequences of SEQ ID NOS: 64-68, 254-264, 365-369, 437-439, 453, 454, 475-478, 480-482, 484, 485, 487, 511, 514, 515, 517-520, 522, 523, 525, 529-531, 535, 536, 538, 541, 544-546, 549, 553-559, 564, 565, 567, 569-573, 579, 587, 588, 592, 597, 598, 602, 604, 605, 608-611, 617, 621 and 622 show less than 75% identity (determined as described above) to sequences in the EMBL database using the FASTA or BLASTN computer algorithms. Similarly, the amino acid sequences of SEQ ID NOS: 183-195, 331-341, 389-393, 458, 459, 463, 497, 498, 503-505, 507-509, 512, 513, 628, 632, 633, 637, 640, 655, 662-666, 668, 672, 673, 676, 679, 683, 685, 688, 691, 693, 694, 702, 703, 706, 707, 710, 711, 713, 714, 717, 721, 722 and 725 show less than 75% identity to sequences in the SwissProt database.

The isolated cDNA sequences encode proteins that influence the growth, differentiation and activation of several cell types, and that may usefully be developed as agents for the treatment and diagnosis of skin wounds, cancers, growth and developmental defects, and inflammatory disease. The utility for certain of the proteins of the present invention, based on similarity to known proteins, is provided in Table 2 below, together with the location of signal peptides and transmembrane domains for certain of the inventive sequences:

15

Table 2
FUNCTIONS OF NOVEL PROTEINS

P/N SEQ ID NO:	A/A SEQ. ID NO.	SIMILARITY TO KNOWN PROTEINS; FUNCTION
64, 372	183, 396	Slit, a secreted molecule required for central nervous system development
65	184	Immunoglobulin receptor family. About 40% of leucocyte membrane polypeptides contain immunoglobulin superfamily domains

P/N	A/A SEQ.	
SEQ ID	ID NO.	SIMILARITY TO KNOWN PROTEINS; FUNCTION
NO:	<u>-</u>	<u> </u>
66,	185,	RIP protein kinase, a serine/threonine kinase that contains a
403	409	death domain to mediate apoptosis
510	512	
67	186	Extracellular protein with epidermal growth factor domain capable of stimulating fibroblast proliferation
68,	187	Transforming growth factor alpha, a protein which binds
437		epidermal growth factor receptor and stimulates growth and mobility of keratinocytes
69	188	DRS protein which has a secretion signal component and whose expression is suppressed in cells transformed by oncogenes
70	189	A33 receptor with immunoglobulin-like domains and is expressed in greater than 95% of colon tumors
71	190	Interleukin-12 alpha subunit, component of a cytokine that is important in the immune defense against intracellular pathogens. IL-12 also stimulates proliferation and differentiation of TH1 subset of lymphocytes
72	191	Tumor Necrosis Factor receptor family of proteins that are involved in the proliferation, differentiation and death of many cell types including B and T lymphocytes.
73	192	Epidermal growth factor family proteins which stimulate growth and mobility of keratinocytes and epithelial cells. EGF is involved in wound healing. It also inhibits gastric acid secretion.
74	193	Fibronectin Type III receptor family. The fibronectin III domains are found on the extracellular regions of cytokine receptors
75.	194	Serine/threonine kinases (STK2_HUMAN) which participate in cell cycle progression and signal transduction
76	195	Immunoglobulin receptor family
254	331	Receptor with immunoglobulin-like domains and homology to A33 receptor which is expressed in greater than 95% of colon tumors
255	332	Epidermal growth factor family proteins which stimulate growth and mobility of keratinocytes and epithelial cells. EGF is involved in wound healing. It also inhibits gastric acid secretion.
256	333	Serine/threonine kinases (STK2_HUMAN) which participate in cell cycle progression and signal transduction

P/N SEQ ID NO:	A/A SEQ. ID NO.	SIMILARITY TO KNOWN PROTEINS; FUNCTION
- 257	334	Contains protein kinase and ankyrin domains. Possible role in cellular growth and differentiation.
258	335	Notch family proteins which are receptors involved in cellular differentiation.
259	336	Extracellular protein with epidermal growth factor domain capable of stimulating fibroblast proliferation.
260, 453	337, 463	Fibronectin Type III receptor family. The fibronectin III domains are found on the extracellular regions of cytokine receptors.
261	338	Immunoglobulin receptor family
262	339	ADP/ATP transporter family member containing a calcium binding site.
263	340	Mouse CXC chemokine family members are regulators of epithelial, lymphoid, myeloid, stromal and neuronal cell migration and cancers, agents for the healing of cancers, neuro-degenerative diseases, wound healing, inflammatory autoimmune diseases like psoriasis, asthma, Crohns disease and as agents for the prevention of HIV-1 of leukocytes
264	341	Nucleotide-sugar transporter family member.
365	389	Transforming growth factor betas (TGF-betas) are secreted covalently linked to latent TGF-beta-binding proteins (LTBPs). LTBPs are deposited in the extracellular matrix and play a role in cell growth or differentiation.
366	390	Integrins are Type I membrane proteins that function as laminin and collagen receptors and play a role in cell adhesion.
367	391	Integrins are Type I membrane proteins that function as laminin and collagen receptors and play a role in cell adhesion.
368	392	Cell wall protein precursor. Are involved in cellular growth or differentiation.
369	393	HT protein is a secreted glycoprotein with an EGF-like domain. It functions as a modulator of cell growth, death or differentiation.
467	489	Myb proto-oncogene (c-Myb), involved in transcription regulation and activation of transcription

P/N	A/A SEQ.	
SEQ ID NO:	ID NO.	SIMILARITY TO KNOWN PROTEINS; FUNCTION
471	493	Chondroitin sulfotransferase, a member of the HNK-1 sulfotransferase family. These molecules are involved in the pathogenesis of arteriosclerosis, and proliferation of arterial smooth muscle cells during development of arteriosclerosis.
472	494	36 kDa nucleolar protein HNP36, a novel growth factor responsive gene expressed in the pituitary and parathyroid glands
475	497	Zinc protease is a matrix metalloproteinase whose activity is directed against components of the extracellular matrix and play an important role in the growth, metastasis and angiogenesis of tumors.
476	498	Diapophytoene dehydrogenase crtn-like molecule. This molecule is similar to the diapophytoene dehydrogenase crt molecule in a major photosynthesis gene cluster from the bacterium <i>Heliobacillus mobilis</i>
477	499	Protocadherin 3 family member, involved in cell to cell interactions.
478	500	Integrins are Type I membrane proteins that function as laminin and collagen receptors and play a role in cell adhesion.
479 .	501	Integrin family member. Integrins are Type I membrane proteins that function as laminin and collagen receptors and play a role in cell adhesion.
480	502	Similar to secreted HT Protein, a secreted glycoprotein with an EGF-like domain. It functions as a modulator of cell growth, death or differentiation.
481	503	Agrin family member: Agrin is produced by motoneurons and induces the aggregation of nicotinic acetylcholine receptors.
482	504	Macrophage Scavenger Receptors bind to a variety of polyanionic ligands and display complex binding characteristics. They have been implicated in various macrophage-associated processes, including atherosclerosis.
483	505	Similar to GARP, a member of the family of leucine-rich repeat-containing proteins involved in platelet-endothelium interactions.
484	506	Epidermal growth factor family proteins which stimulate growth and mobility of keratinocytes and epithelial cells. EGF is involved in wound healing. It also inhibits gastric

P/N	A/A SEQ.	
SEQ ID NO:	ID NO.	SIMILARITY TO KNOWN PROTEINS; FUNCTION
110.		acid secretion.
485	507	Colony stimulating growth factor family.
486	508	Cytokine receptors
487	509	IL17 Receptor to Interleukin 17 (IL17), a T cell derived cytokine that may play a role in initiation or maintenance of the inflammatory response.
. 438	458	MEGF6, a protein containing multiple EGF-like-domains.
439	459	Protein kinase family member involved in signal transduction.
454		Peroxisomal calcium-dependent solute carrier, a new member of the mitochondrial transporter superfamily.
511	513	Serine/threonine kinase NEK1 is a NIMA-related protein kinase that phosphorylates serines and threonines, but also possesses tyrosine kinase activity. NEK1 has been implicated in the control of meiosis and belongs to the NIMA kinase subfamily.
514	624 62	eHomologue isolated from rat dermal papilla of integrin alpha-11/beta-1 that is involved in muscle development and maintaining integrity of adult muscle and other adult tissues. Integrin alpha-11/beta-1 is a receptor for collagen and belongs to the integrin alpha chain family.
516	625	This is a secreted molecule isolated from rat dermal papillae with a signal peptide at the N-terminus (amino acid residues 1 to 21; nucleotides 42 to 104).
517	626	Homologue isolated from a rat dermal papilla library of OASIS (old astrocyte specifically-induced substance) and that plays a role in regulation of the response of astrocytes to inflammation and trauma of the central nervous system (CNS) during gliosis. The OASIS gene encodes a putative transcription factor belonging to the cyclic AMP responsive element binding protein/activating transcription factor (CREB/ATF) gene family (Honma et al., Brain Res. Mol. Brain Res. 69:93-103, 1999).

P/N	A/A SEQ.	16
SEQ ID NO:	ID NO.	SIMILARITY TO KNOWN PROTEINS; FUNCTION
519	628	This is a secreted molecule isolated from rat dermal papillae with a signal peptide at the N-terminus (amino acid residues 1 to 24; nucleotides 50 to 121).
520	630	This is a secreted molecule isolated from rat dermal papillae with a signal peptide at the N-terminus (amino acid residues 1 to 35; nucleotides 67 to 171).
523	633	This is a secreted molecule isolated from rat dermal papillae with a signal peptide at the N-terminus (amino acid residues 1 to 17; nucleotides 3 to 53).
524	634	This is a secreted molecule isolated from rat dermal papillae with a signal peptide at the N-terminus (amino acid residues 1 to 20; nucleotides 13 to 72).
525, 534	635, 644	Homologue isolated from a rat dermal papilla library of leucyl-specific aminopeptidase, PILS-AP and that plays role in many physiological processes as a substrate-specific peptidase. PILS is a new member of the M1 famile of Zndependent aminopeptidases that comprises members of closely related enzymes which are known to be involved in a variety of physiologically important processes.
526	636	This is a secreted molecule isolated from rat dermal papillae with a signal peptide at the N-terminus (amino acid residues 1 to 26; nucleotides 114 to 191).
527	637	This is a secreted molecule isolated from rat dermal papillae with a signal peptide at the N-terminus (amino acid residues 1 to 26; nucleotides 23 to 100).
529	639	This is a secreted molecule isolated from rat dermal papillae with a signal peptide at the N-terminus (amino acid residues 1 to 17; nucleotides 37 to 87).
530	640	This is a homologue isolated from a rat dermal papilla library of a maturase that is involved in RNA splicing.
531	641	This is a secreted molecule isolated from rat dermal papillae with a signal peptide at the N-terminus (amino acid residues 1 to 17; nucleotides 180 to 230).
532	642	This is a secreted molecule isolated from rat dermal papillae with a signal peptide at the N-terminus (amino acid residues 1 to 32; nucleotides 245 to 340).
535	645	This is a secreted molecule isolated from rat dermal papillae with a signal peptide at the N-terminus (amino acid residues 1 to 25; nucleotides 188 to 333).

P/N	A/A SEQ.	· · · · · · · · · · · · · · · · · · ·
SEQ ID NO:	ID NO.	SIMILARITY TO KNOWN PROTEINS; FUNCTION
536	646	This is a secreted molecule isolated from rat dermal papillae with a signal peptide at the N-terminus (amino acid residues 1 to 21; nucleotides 185 to 247).
537	647	This is a secreted molecule isolated from rat dermal papillae with a signal peptide at the N-terminus (amino acid residues 1 to 24; nucleotides 129 to 200).
541	651	This is a homologue isolated from a rat dermal papilla library of a hepatoma-derived growth factor (HDGF) that is involved in stimulation of cell proliferation.
542	652	This is a receptor-like molecule isolated from rat dermal papillae with two transmembrane domains (amino acid residues 20 to 40 and 58 to 78.
545	655	This is a homologue isolated from a rat dermal papilla library of Link protein (LP) and that is involved in bone formation. LP plays an essential role in endochondral bone formation by stabilizing the supramolecular assemblies of aggrecan and hyaluronan (Deak et al., Cytogenet. Cell Genet. 87:75-79, 1999).
548	658	This is a homologue isolated from a rat dermal papilla library of thrombospondin (TSP). It is a secreted protein with a signal peptide in amino acid residues 1 to 18 (nucleotides 210 to 263). TSP is an extracellular matrix glycoprotein whose expression has been associated with a variety of cellular processes including growth and embryogenesis (Laherty et al., J. Biol. Chem. 267:3,274-3,281, 1992).
553	662	This is a receptor-like molecule isolated from rat dermal papillae with a transmembrane domain (amino acid residues 434 to 454.
554	663	This is a receptor-like molecule isolated from rat dermal papillae with a transmembrane domain (amino acid residues 546 to 566.
555	664	This is a homologue isolated from a rat dermal papilla library of B7-like mouse GL50 (mGL50). It is a receptor-like molecule with a signal peptide in residues 1 to 24 (nucleotides 149 to 220) and a transmembrane domain in amino acid residues 262 to 282. GL50 is a specific ligand for the ICOS receptor and this interaction functions in lymphocyte costimulation (Ling et al., J. Immunol. 164:1,653-1,657, 2000).

P/N SEQ ID	A/A SEQ. ID NO.	SIMILARITY TO KNOWN PROTEINS; FUNCTION	
NO:			
557, 558, 561-572	666, 667, 670-678	These molecules are differentially expressed in stem cells but not in mature keratinocytes and are involved in developmental processes. They may be employed for diagnosis of tumors with an immature phenotype.	
559	668	This is a homologue isolated from a mouse stem cell library of ABSENT IN MELANOMA 1 protein AIM1 and that can be used for diagnosis of tumours with an immature phenotype. AIM1 is a novel gene whose expression is associated with the experimental reversal of tumorigenicity of human malignant melanoma and belongs to the betagamma-crystallin superfamily (Ray et al., Proc. Natl. Acad. Sci. USA 94:3,229-3,234, 1997)	
560	669	Homologue isolated from a mouse stem cell library of endothelin-convertin enzyme 2 (ECE-2) and that can be used for diagnosis of tumours with an immature phenotype. Endothelins (ET) are a family of potent vasoactive peptides that are produced from biologically inactive intermediates, termed big endothelins, via a proteolytic processing at Trp21-Val/Ile22. ECE-2, that produces mature ET-1 from big ET-1 both in vitro and in transfected cells. ECE-2 acts as an intracellular enzyme responsible for the conversion of endogenously synthesized big ET-1 at the trans-Golgi network, where the vesicular fluid is acidified (Emoto and Yanagisawa, J. Biol. Chem. 270:15,262-15,268, 1995).	
573	679	Mouse homologue of EGF-like molecule containing mucin-like hormone receptor 2 (EMR2). The isolated molecule contains three transmembrane regions: amino acid residues 20 to 40, 66 to 86 and 92 to 112. The epidermal growth factor (EGF)-TM7 proteins [EMR1 and EMR2, F4/80, and CD97] constitute a recently defined class B GPCR subfamily and are predominantly expressed on leukocytes. These molecules possess N-terminal EGF-like domains coupled to a seven-span transmembrane (7TM) moiety via a mucin-like spacer domain (Lin et al., Genomics 67:188-200, 2000).	
574	680	This is a murine secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 17; nucleotides 238 to 288).	
575	681	Mouse homologue of a glucocortocoid-inducible protein GIS5 with a signal peptide at the N-terminus (amino acid	

P/N SEQ ID	A/A SEQ. ID NO:	SIMILARITY TO KNOWN PROTEINS; FUNCTION	
NO:			
		residues 1 to 17; nucleotides 56-106).	
576	682	This is a murine surface receptor-like molecule with a signal peptide at the N-terminus (amino acid residues 1 to 17; nucleotides 1179 to 199) and a transmembrane domain (amino acid residues 179 to 199).	
577	683	This is a murine secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 16; nucleotides 55 to 102).	
578	684	This is a murine secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 22; nucleotides 12 to 77).	
579	685	This is a murine secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 17; nucleotides 82 to 132).	
580	686	This is a murine secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 20; nucleotides 20 to 79).	
581	687	This is a murine receptor-like molecule with transmembrane domains at amino acid residues 50 to 70; 84 to 104; 116 to 136 and 179 to 198.	
585	691	This is a murine secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 20; nucleotides 260 to 319).	
586	695	This is a murine secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 22; nucleotides 295 to 360).	
587	693	This is a mouse homologue of serotransferrin, also known as siderophilin or beta-1-metal binding globulin) and that is involved in iron transport. This homologue is a secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 19; nucleotides 43 to 99). Transferrins are iron binding transport proteins which can bind two atoms of ferric iron in association with the binding of an anion, usually bicarbonate. It is responsible for the transport of iron from sites of absorption and heme degradation to those of storage and utilization. Serum transferrin may also have a further role in stimulating cell proliferation. Transferrin belongs to the transferrin family.	

P/N	A/A SEQ.	SIMILARITY TO KNOWN PROTEINS; FUNCTION	
SEQ ID NO:	ID NO.		
589	695	This is a murine secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 25; nucleotides 1 to 75).	
. 592	697	This is a murine receptor-like molecule with a transmembrane domain in amino acid residues 52 to 72.	
593	698	Mouse homologue of channel inducing factor (CHIF) that plays a role in ion transport. The mouse homologue has a signal peptide at the N-terminus of the predicted polypeptide (amino acid residues 1 to 20; nucleotides 102 to 161) and a transmembrane domain (amino acid residues 38 to 58). CHIF evokes a potassium channel activity (Attali et al., Proc. Natl. Acad. Sci. USA 92:6092-6096, 1995).	
595	700	Homologue of hyaluronan receptor LYVE-1 that plays a role in hyalyronan uptake. This mouse homologue has the characteristic signal peptide and transmembrane domain of a receptor. A signal peptide was identified in the isolated molecule in amino acid residues 1 to 18 (nucleotides 62 to 115) and the transmembrane domain in amino acid residues 233 to 253. The extracellular matrix glycosaminoglycan hyaluronan (HA) is an abundant component of skin and mesenchymal tissues where it facilitates cell migration during wound healing, inflammation, and embryonic morphogenesis. Both during normal tissue homeostasis and particularly after tissue injury, HA is mobilized from these sites through lymphatic vessels to the lymph nodes where it is degraded before entering the circulation for rapid uptake by the liver. LYVE-1 is a receptor for HA on the lymph vessel wall and plays a role in the transport of HA from tissue to lymph (Banerji et al., J. Cell Biol. 144:789-801,1999).	
596	701	This is a murine secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 21; nucleotides 7 to 69).	
598	703	Homologue of tumor-associated glycoprotein E4 (TAA1 or TAGE4) that belongs to the immunoglobulin superfamily. This molecule has a signal peptide at the N-terminus (amino acid residues 1 to 24; nucleotides 71 to 142) and is therefore a secreted protein.	

	144 0770	
P/N SEQ ID NO:	A/A SEQ. ID NO.	SIMILARITY TO KNOWN PROTEINS; FUNCTION
599	704	Homologue of the LUNX protein, also known as nasopharyngeal carcinoma-related protein, tracheal epithelium enriched protein or plunc, that is expressed in epithelial cells in the airways. It has a signal peptide at the N-terminus (amino acid residues 1 to 19; nucleotides 39 to 95). Expression of LUNX is restricted to the trachea, upper airway, nasopharyngeal epithelium and salivary gland (Bingle and Bingle, Biochim. Biophys. Acta 1493:363-367, 2000).
600	705	This is a murine secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 23; nucleotides 136 to 204.
601	706	Homologue of prenylcysteine lyase (EC 4.4.1.18) and that is involved in degradation of prenylated proteins. It has a signal peptide at the N-terminus (amino acid residues 1 to 28; nucleotides 22 to 105). Prenylcysteine lyase is a specific enzyme involved in the final step of prenylcysteine metabolism in mammalian cells. The enzyme does not require NADPH as cofactor for prenylcysteine degradation, thus distinguishing it from cytochrome P450- and flavincontaining monooxygenases that catalyze S-oxidation of thioethers (Zhang et al., J. Biol. Chem. 274:35802-35808, 1999).
605	710	Homologue of endoplasmin, endoplasmic reticulum protein 99 (ERp99), 94 kDa glucose-regulated protein (GRP94) and polymorphic tumor rejection antigen 1 (gp96). The isolated molecule has a signal peptide at the N-terminus (amino acid residue 1 to 21; nucleotides 1867 to 206). ERp99 is an abundant, conserved transmembrane glycoprotein of the endoplasmic reticulum membrane and homologous to the 90-kDa heat shock protein (hsp90) and the 94-kDa glucose regulated protein (GRP94) (Mazzarella and Green, J. Biol. Chem. 262:8875-8883, 1987).
606	711	Homologue of PILRalpha, formerly known as inhibitory receptor PIRIIalpha and that is involved in signal transduction in various cellular processes. This molecule contains a signal peptide at the N-terminal end (amino acid residues 1-21 and nucleotides 47 to 139) and a transmembrane domain at amino acid residues 191 to 211. SHP-1-mediated dephosphorylation of protein tyrosine

P/N	A/A SEQ.	
SEQ ID	ID NO.	SIMILARITY TO KNOWN PROTEINS; FUNCTION
NO:		
		residues is central to the regulation of several cell signaling
	i i	pathways. PILRalpha, a novel immunoreceptor tyrosine-
		based inhibitory motif-bearing protein, recruits SHP-1 upon
	1	tyrosine phosphorylation and is paired with the truncated counterpart PILRbeta (Mousseau et al., J. Biol. Chem.
		275:4467-4474, 2000).
607	712	This is a murine secreted molecule with a signal peptide at
}	'	the N-terminus (amino acid residues 1 to 18; nucleotides 38
		to 91.
609	714	Homologue of retinal short-chain dehydrogenase/reductase
		retSDR2 that plays a role on retinal metabolism. It has a
	٠,	signal peptide at the N-terminus at amino acid residues 1 –
		29 (nucleotides 302 to 388). Retinol dehydrogenases
İ		(RDH) catalyze the reduction of all-trans-retinal to all-trans- retinol within the photoreceptor outer segment in the
	ł	regeneration of bleached visual pigments (Haeseleer et al.,
İ		J. Biol. Chem. 273:21790-21799, 1998)
612	717	This is a murine secreted molecule with a signal peptide at
	1	the N-terminus (amino acid residues 1 to 22; nucleotides 6
		to 71.
613	718	This is a murine secreted molecule with a signal peptide at
		the N-terminus (amino acid residues 1 to 25; nucleotides
	700	210 to 284.
615	720	This is a murine secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 16; nucleotides 70
		to 117.
616	721	This is a murine secreted molecule with a signal peptide at
		the N-terminus (amino acid residues 1 to 18; nucleotides 1
		to 54.

The locations of open reading frames (ORFs) within certain of the inventive cDNA sequences are shown in Table 3, below.

Table 3

LOCATION OF OPEN READING FRAMES

SEQ ID NO		SEQ ID NO
Polynucleotide	ORF	Polypeptide
514	1-2,067	624
515	2-730	625
516	42-1,772	626
517	1-681	627
. 518	170-416	628
519	50-770	629
520	67-708	630
521	110-613	631
522	41-457	632
523	3-230	633
524	13-573	634
525	64-2,856	635
526	114-599	636
527	23-520	637
528	953-1,138	638
529	37-687	639
530	145-366	640
531	180-1,508	643
532	245-442	642
533	125-595	643 .
534	64-2,856	644
535	188-727	645
536	185-1,081	646
537	129-308	647
538	32-853	648
539	2-268	649
540	3-875	650
541	284-892	651
542	37-276	652
543	127-1,794	653
544	1-735	654
545	142-939	655
546	51-1,082	656
547	143-328	657
548	210-3,728	658
549	26-1,354	659
551	1,236-1,892	660
552	853-1,178	661

SEQ ID NO	0777	SEQ ID NO
Polynucleotide	ORF	Polypeptide
. 553	54-1,356	662
554	637-2,244	663
555	149-1,072	664
556	18-449	665 .
557	275-1,171	666
558	453-1,133	667
559	104-2,449	668
560	463-687	669
562	1-1,107	670
563	2-883	671
564	188-2,902	672
565	3-524	673
567	2,584-3,996	674
569	1-960	675
570	315-599	676
571	1-414	677
572	806-1,912	678
. 573	120-752-	679
574	2381,359	680
575	56-1,456	681
576	13-645	682
577	55-1,323	683
578	12-698	684
579	82-810	685
580	20-586	686
581	65-808	687
582	369-761	688
583	1-769	689
584	164-1,321	690
585	260-1,489	691
586	295-1,131	692
587	43-2,136	. 693
588	1-1,203	694
589	1-525	695
591	1-584	696
592	1-522	697
593	102-368	698
594	1-517	699

SEQ ID NO		SEQ ID NO
Polynucleotide	ORF	Polypeptide
595	62-1,018	700
596	7-282	701
597	1-736	702
598	71-1,297	703
599	39-875	704
600	136-930	705
601	22-1,539	706
602	69-521	707
603	104-448	. 708
604	1-399	709
605	3,068-5,476	710
606	47-721	711
607	38-439	712
608	1-1,656	713
609	302-1,327	714
610	845-1,447	715
611	975-1,375	716
612	6-272	717
613	210-464	718
614	462-869	719 .
615	70-459	720
616	1-1,107	721
617	1-349	722
618	93-528	723
621	380-1,033	724
622	43-2,115	725

The cDNA sequences of SEQ ID NO: 514, 515, 516, 557, 558, 559, 560, 561, 567, 568, 619 and 621 are extended sequences of SEQ ID NO: 479, 480, 353, 91, 108, 82, 92, 81, 105, 90, 362 and 360, respectively. SEQ ID NO: 516, 520, 521, 523, 525, 526, 529, 534-536, 541-543, 546, 548, 549, 557, 574, 575, 577-581, 584-587, 589, 593, 595, 596, 598-601, 605, 607, 609, 610, 614, 616 and 622 represent full-length cDNA sequences.

The polynucleotide sequences of SEQ ID NOS: 77-117, 265-267, 404-405 and 557-611 are differentially expressed in either keratinocyte stem cells (KSCL) or in transit amplified cells (TRAM) on the basis of the number of times these sequences exclusively appear in either one of the above two libraries; more than 9 times in one and none in the other (Audic S. and Claverie J-M, *Genome Research*, 7:986-995, 1997). The sequences of SEQ ID NOS: 77-89, 265-267 and 365-369 were determined to have less than 75% identity to sequences in the EMBL database using the computer algorithm FASTA or BLASTN, as described above. The polypeptide sequences encoded by the cDNA sequences of SEQ ID NO: 77-117, 265-267, 404-405 and 557-611 are provided in SEQ ID NOS: 666-718. The amino acid sequences of SEQ ID NOS: 666, 668, 669, 671-673, 675, 676, 679, 682, 683, 685, 688, 690, 691, 693, 694, 702, 703, 706-708, 710, 711, 713 and 714 show less than 75% identity to sequences in the SwissProt database.

The polypeptides encoded by these polynucleotide sequences have utility as markers for identification and isolation of these cell types, and antibodies against these proteins may be usefully employed in the isolation and enrichment of these cells from complex mixtures of cells. Isolated polynucleotides and their corresponding proteins exclusive to the stem cell population can be used as drug targets to cause alterations in regulation of growth and differentiation of skin cells, or in gene targeting to transport specific therapeutic molecules to skin stem cells.

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## Example 3

# ISOLATION AND CHARACTERIZATION OF THE HUMAN HOMOLOG OF MUTRI

The human homolog of muTR1 (SEQ ID NO: 68), obtained as described above in Example 1, was isolated by screening 50,000 pfu's of an oligo dT primed HeLa cell cDNA library. Plaque lifts, hybridization, and screening were performed using standard molecular biology techniques (Sambrook, J, Fritsch, EF and Maniatis, T, eds., *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor: New York, 1989). The determined cDNA sequence of the isolated human homolog (huTR1) is provided in SEQ ID NO: 118, with the corresponding

polypeptide sequence being provided in SEQ ID NO: 196. The library was screened using an [ $\alpha$  <sup>32</sup>P]-dCTP labeled double stranded cDNA probe corresponding to nucleotides 1 to 459 of the coding region within SEQ ID NO: 118.

\*\*The polypeptide sequence of huTR1 has regions similar to Transforming Growth Factor-alpha, indicating that this protein functions like an epidermal growth factor (EGF). EGF family members exist in a functional form as small peptides. Alignment of the functional peptides of the EGF family with SEQ ID NO: 196 revealed that an internal segment of SEQ ID NO: 196 (amino acids 54-104) shows greater than 40% identity to the active peptides of EGF, TGF-alpha and Epiregulin. The active peptides of the EGF family are sufficient for activity and contain several conserved residues critical for the maintenance of this activity. These residues are retained in huTR1. This EGF-like protein will serve to stimulate keratinocyte growth and motility, and to inhibit the growth of epithelial-derived cancer cells. This novel gene and its encoded protein may thus be used as agents for the healing of wounds and regulators of epithelial-derived cancers.

## Analysis of RNA transcripts by Northern Blotting

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Northern analysis to determine the size and distribution of mRNA for huTR1 was performed by probing human tissue mRNA blots (Clontech) with a probe comprising nucleotides 93-673 of SEQ ID NO: 118, radioactively labeled with  $[\alpha^{32}P]$ -dCTP. Prehybridization, hybridization, washing and probe labeling were performed as described in Sambrook, *et al.*, *Ibid.* mRNA for huTR1 was 3.5-4kb in size and was observed to be most abundant in heart and placenta, with expression at lower levels being observed in spleen, thymus, prostate and ovary (Fig. 1).

The high abundance of mRNA for huTR1 in the heart and placenta indicates a role for huTR1 in the formation or maintenance of blood vessels, as heart and placental tissues have an increased abundance of blood vessels, and therefore endothelial cells, compared to other tissues in the body. This, in turn, demonstrates a role for huTR1 in angiogenesis and vascularization of tumors. This is supported by the ability of

Transforming Growth Factor-alpha and EGF to induce *de novo* development of blood vessels (Schreiber, *et al.*, *Science* 232:1250-1253, 1986) and stimulate DNA synthesis in endothelial cells (Schreiber, *et al.*, *Science* 232:1250-1253, 1986), and their over-expression in a variety of human tumors.

### Purification of muTR1 and huTR1

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Polynucleotides 177-329 of muTR1 (SEQ ID NO: 268), encoding amino acids 53-103 of muTR1 (SEQ ID NO: 342), and polynucleotides 208-360 of huTR1 (SEQ ID NO: 269), encoding amino acids 54-104 of huTR1 (SEQ ID NO: 343), were cloned into the bacterial expression vector pProEX HT (BRL Life Technologies), which contains a bacterial leader sequence and N-terminal 6xHistidine tag. These constructs were transformed into competent XL1-Blue *E. coli* as described in Sambrook et al., *Ibid*.

Starter cultures of these recombinant XL1-Blue *E. coli* were grown overnight at  $37^{\circ}$ C in Terrific broth containing  $100 \mu g/ml$  ampicillin. This culture was spun down and used to inoculate 500 ml culture of Terrific broth containing  $100 \mu g/ml$  ampicillin. Cultures were grown until the OD<sub>595</sub> of the cells was between 0.4 and 0.8, whereupon IPTG was added to 1 mM. Cells were induced overnight and bacteria were harvested by centrifugation.

Both the polypeptide of muTR1 (SEQ ID NO: 342; referred to as muTR1a) and that of huTR1 (SEQ ID NO: 343; referred to as huTR1a) were expressed in insoluble inclusion bodies. In order to purify the polypeptides muTR1a and huTR1a, bacterial cell pellets were re-suspended in lysis buffer (20 mM Tris-HCl pH 8.0, 10 mM beta mercaptoethanol, 1 mM PMSF). To the lysed cells, 1% NP40 was added and the mix incubated on ice for 10 minutes. Lysates were further disrupted by sonication on ice at 95W for 4 x 15 seconds and then centrifuged for 15 minutes at 14,000 rpm to pellet the inclusion bodies.

The resulting pellet was re-suspended in lysis buffer containing 0.5% w/v CHAPS and sonicated on ice for 5-10 seconds. This mix was stored on ice for 1 hour, centrifuged at 14,000 rpm for 15 minutes at 4 °C and the supernatant discarded. The pellet was once

more re-suspended in lysis buffer containing 0.5% w/v CHAPS, sonicated, centrifuged and the supernatant removed as before. The pellet was re-suspended in solubilizing buffer (6 M Guanidine HCl, 0.5 M NaCl, 20 mM Tris HCl, pH 8.0), sonicated at 95 W for 4 x 15 seconds and then centrifuged for 20 minutes at 14,000 rpm and 4 °C to remove debris. The supernatant was stored at 4 °C until use.

Polypeptides muTR1a and huTR1a were purified by virtue of the N-terminal 6x Histidine tag contained within the bacterial leader sequence, using a Nickel-Chelating Sepharose column (Amersham Pharmacia, Uppsala, Sweden) and following the manufacturer's recommended protocol. In order to refold the proteins once purified, the protein solution was added to 5x its volume of refolding buffer (1 mM EDTA, 1.25 mM reduced glutathione, 0.25 mM oxidised glutathione, 20 mM Tris-HCl, pH 8.0) over a period of 1 hour at 4 °C. The refolding buffer was stirred rapidly during this time, and stirring continued at 4 °C overnight. The refolded proteins were then concentrated by ultrafiltration using standard protocols.

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#### Biological Activities of Polypeptides muTR1a and huTR1a

muTR1 and huTR1 are novel members of the EGF family, which includes EGF, TGFo, epiregulin and others. These growth factors are known to act as ligands for the EGF receptor. The pathway of EGF receptor activation is well documented. Upon binding of a ligand to the EGF receptor, a cascade of events follows, including the phosphorylation of proteins known as MAP kinases. The phosphorylation of MAP kinase can thus be used as a marker of EGF receptor activation. Monoclonal antibodies exist which recognize the phosphorylated forms of 2 MAP kinase proteins – ERK1 and ERK2.

In order to examine whether purified polypeptides of muTR1a and huTR1a act as a ligand for the EGF receptor, cells from the human epidermal carcinoma cell line A431 (American Type Culture Collection, No. CRL-1555, Manassas, Virginia) were seeded into 6 well plates, serum starved for 24 hours, and then stimulated with purified muTR1a or huTR1a for 5 minutes in serum free conditions. As a positive control, cells were

stimulated in the same way with 10 to 100 ng/ml TGF-alpha or EGF. As a negative control, cells were stimulated with PBS containing varying amounts of LPS. Cells were immediately lysed and protein concentration of the lysates estimated by Bradford assay. 15 µg of protein from each sample was loaded onto 12% SDS-PAGE gels. The proteins were then transferred to PVDF membrane using standard techniques.

For Western blotting, membranes were incubated in blocking buffer (10mM Tris-HCl, pH 7.6, 100 mM NaCl, 0.1% Tween-20, 5% non-fat milk) for 1 hour at room temperature. Rabbit anti-Active MAP kinase pAb (Promega, Madison, Wisconsin) was added to 50 ng/ml in blocking buffer and incubated overnight at 4 °C. Membranes were washed for 30 mins in blocking buffer minus non-fat milk before being incubated with anti-rabbit IgG-HRP antibody, at a 1:3500 dilution in blocking buffer, for 1 hour at room temperature. Membranes were washed for 30 minutes in blocking buffer minus non-fat milk, then once for 5 minutes in blocking buffer minus non-fat milk and 0.1% Tween-20. Membranes were then exposed to ECL reagents for 2 min, and then autoradiographed for 5 to 30 min.

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As shown in Fig. 2, both muTR1a and huTR1a were found to induce the phosphorylation of ERK1 and ERK2 over background levels, indicating that muTR1 and huTR1 act as ligands for a cell surface receptor that activates the MAP kinase signaling pathway, possibly the EGF receptor. As shown in Fig. 11, huTR1a was also demonstrated to induce the phosphorylation of ERK1 and ERK2 in CV1/EBNA kidney epithelial cells in culture, as compared with the negative control. These assays were conducted as described above. This indicates that huTR1a acts as a ligand for a cell surface receptor that activates the MAP kinase signaling pathway, possibly the EGF receptor in HeLa and CV1/EBNA cells.

The ability of muTR1a to stimulate the growth of neonatal foreskin (NF) keratinocytes was determined as follows. NF keratinocytes derived from surgical discards were cultured in KSFM (BRL Life Technologies) supplemented with bovine pituatary extract (BPE) and epidermal growth factor (EGF). The assay was performed in 96 well flat-bottomed plates in 0.1 ml unsupplemented KSFM. MuTR1a, human

transforming growth factor alpha (huTGF $\alpha$ ) or PBS-BSA was titrated into the plates and 1 x 10<sup>3</sup> NF keratinocytes were added to each well. The plates were incubated for 5 days in an atmosphere of 5% CO<sub>2</sub> at 37<sup>0</sup>C. The degree of cell growth was determined by MTT dye reduction as described previously (*J. Imm. Meth.* 93:157-165, 1986). As shown in Fig. 3, both muTR1a and the positive control human TGF $\alpha$  stimulated the growth of NF keratinocytes, whereas the negative control, PBS-BSA, did not.

The ability of muTR1a and huTR1a to stimulate the growth of a transformed human keratinocyte cell line, HaCaT, was determined as follows. The assay was performed in 96 well flat-bottomed plates in 0.1 ml DMEM (BRL Life Technologies) supplemented with 0.2% FCS. MuTR1a, huTR1a and PBS-BSA were titrated into the plates and 1 x10<sup>3</sup> HaCaT cells were added to each well. The plates were incubated for 5 days in an atmosphere containing 10% CO<sub>2</sub> at 37<sup>0</sup>C. The degree of cell growth was determined by MTT dye reduction as described previously (*J. Imm. Meth.* 93:157-165, 1986). As shown in Fig. 4, both muTR1a and huTR1a stimulated the growth of HaCaT cells, whereas the negative control PBS-BSA did not.

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The ability of muTR1a and huTR1a to inhibit the growth of A431 cells was determined as follows. Polypeptides muTR1a (SEQ ID NO: 342) and huTR1a (SEQ ID NO: 343) and PBS-BSA were titrated as described previously (*J. Cell. Biol.* 93:1-4, 1982), and cell death was determined using the MTT dye reduction as described previously (*J. Imm. Meth.* 93:157-165, 1986). Both muTR1a and huTR1a were found to inhibit the growth of A431 cells, whereas the negative control PBS-BSA did not (Fig. 5).

These results indicate that muTR1 and huTR1 stimulate keratinocyte growth and motility, inhibit the growth of epithelial-derived cancer cells, and play a role in angiogenesis and vascularization of tumors. This novel gene and its encoded protein may thus be developed as agents for the healing of wounds, angiogenesis and regulators of epithelial-derived cancers.

### Upregulation of huTR1 and mRNA expression

HeLa cells (human cervical adenocarcinoma) were seeded in 10 cm dishes at a concentration of 1 x 10<sup>6</sup> cells per dish. After incubation overnight, media was removed and replaced with media containing 100 ng/ml of muTR1, huTR1, huTGFα, or PBS as a negative control. After 18 hours, media was removed and the cells lysed in 2 ml of TRIzol reagent (Gibco BRL Life Technologies, Gaithersburg, Maryland). Total RNA was isolated according to the manufacturer's instructions. To identify mRNA levels of huTR1 from the cDNA samples, 1 μl of cDNA was used in a standard PCR reaction. After cycling for 30 cycles, 5 μl of each PCR reaction was removed and separated on a 1.5% agarose gel. Bands were visualized by ethidium bromide staining. As can be seen from Fig. 12, both mouse and human TR1 up-regulate the mRNA levels of huTR1 as compared with cells stimulated with the negative control of PBS. Furthermore, TGFα can also up-regulate the mRNA levels of huTR1.

These results indicate that TR1 is able to sustain its own mRNA expression and subsequent protein expression, and thus is expected to be able to contribute to the progression of diseases such as psoriasis where high levels of cytokine expression are involved in the pathology of the disease. Furthermore, since  $TGF\alpha$  can up-regulate the expression of huTR1, the up-regulation of TR1 mRNA may be critical to the mode of action of  $TGF\alpha$ .

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### Serum response element reporter gene assay

The serum response element (SRE) is a promoter element required for the regulation of many cellular immediate-early genes by growth. Studies have demonstrated that the activity of the SRE can be regulated by the MAP kinase signaling pathway. Two cell lines, PC12 (rat pheochromocytoma – neural tumor) and HaCaT (human transformed keratinocytes), containing eight SRE upstream of an SV40 promotor and luciferase reporter gene were developed in-house. 5 x 10<sup>3</sup> cells were aliquoted per well of 96 well plate and grown for 24 hours in their respective media. HaCaT SRE cells were grown in 5% fetal bovine serum (FBS) in D-MEM supplemented with 2mM L-glutamine (Sigma,

St. Louis, Missouri), 1mM sodium pyruvate (BRL Life Technologies), 0.77mM L-asparagine (Sigma), 0.2mM arginine (Sigma), 160mM penicillin G (Sigma), 70mM dihydrostreptomycin (Roche Molecular Biochemicals, Basel, Switzerland), and 0.5 mg/ml geneticin (BRL Life Technologies). PC12 SRE cells were grown in 5% fetal bovine serum in Ham F12 media supplemented with 0.4 mg/ml geneticin (BRL Life Technologies). Media was then changed to 0.1% FBS and incubated for a further 24 hours. Cells were then stimulated with a titration of TR1 from 1 µg/ml. A single dose of basic fibroblast growth factor at 100 ng/ml (R&D Systems, Minneapolis, Minnesota) or epidermal growth factor at 10 ng/ml (BRL Life Technologies) was used as a positive control. Cells were incubated in the presence of muTR1 or positive control for 6 hours, washed twice in PBS and lysed with 40 µl of lysis buffer (Promega). 10 µl was transferred to a 96 well plate and 10 µl of luciferase substrate (Promega) added by direct injection into each well by a Victor<sup>2</sup> fluorimeter (Wallac), the plate was shaken and the luminescence for each well read at 3x1 sec Intervals. Fold induction of SRE was calculated using the following equation: Fold induction of SRE = Mean relative luminescence of agonist/Mean relative luminescence of negative control.

As shown in Fig. 13, muTR1 activated the SRE in both PC-12 (Fig. 13A) and HaCaT (Fig. 13B) cells. This indicates that HaCaT and PC-12 cells are able to respond to muTR1 protein and elicit a response. In the case of HaCaT cells, this is a growth response. In the case of PC-12 cells, this may be a growth, a growth inhibition, differentiation, or migration response. Thus, TR1 may be important in the development of neural cells or their differentiation into specific neural subsets. TR1 may also be important in the development and progression of neural tumors.

#### 5 Inhibition by the EGF receptor assay

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The HaCaT growth assay was conducted as previously described, with the following modifications. Concurrently with the addition of EGF and TR1 to the media, anti-EGF Receptor (EGFR) antibody (Promega, Madison, Wisconsin) or the negative

control antibody, mouse IgG (PharMingen, San Diego, California), were added at a concentration of 62.5 ng/ml.

As seen in Fig. 14, an antibody which blocks the function of the EGFR inhibited the mitogenicity of TR1 on HaCaT cells. This indicates that the EGFR is crucial for transmission of the TR1 mitogenic signal on HaCaT cells. TR1 may bind directly to the EGF receptor. TR1 may also bind to any other members of the EGFR family (for example, ErbB-2, -3, and/or -4) that are capable of heterodimerizing with the EGFR.

#### Splice variants of huTR1

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A variant of huTR1 was isolated from the same library as huTR1, following the same protocols. The sequence referred to as huTR1-1 (also known as TR1δ) is a splice variant of huTR1 and consists of the ORF of huTR1 minus amino acids 15 to 44 and 87 to 137. These deletions have the effect of deleting part of the signal sequence and following amino terminal linker sequence, residues following the second cysteine residue of the EGF motif and the following transmembrane domain. However, cysteine residue 147 (huTR1 ORF numbering) may replace the deleted cysteine and thus the disulphide bridges are likely not affected. Therefore, huTR1-1 is an intracellular form of huTR1. It functions as an agonist or an antagonist to huTR1 or other EGF family members, including EGF and TGFα. The determined nucleotide sequence of huTR1-1, is given in SEQ ID NO: 412, with the corresponding amino acid sequence being provided in SEQ ID NO: 415.

Four additional splice variants of huTr1 were isolated by PCR on first strand cDNA made from RNA isolated from HeLa cells by standard protocols. These splice variants of huTR1 are referred to as TR1-2 (also known as TR1 $\beta$ ), TR1-3 (also known as TR1 $\gamma$ ), TR1 $\epsilon$  and TR1 $\phi$ .

TR1-2 consists of the ORF of huTR1 minus amino acids 95 to 137. This deletion has the effect of deleting the transmembrane domain. Therefore TR1-2 is a secreted form of huTR1 and binds with equal or greater affinity to the TR1 receptor as huTR1, since the EGF domain remains intact. It functions as an agonist or an antagonist to huTR1 or other

EGF family members, including EGF and TGF $\alpha$ . The determined cDNA sequence of TR1-2 is given in SEQ ID NO: 410 and the corresponding amino acid sequence in SEQ ID NO: 413.

TR1-3 consists of the ORF of huTR1 minus amino acids 36 to 44 and amino acids 86 to 136. These deletions have the effect of deleting part of the amino terminal linker sequence, residues following the second cysteine of the EGF motif and the following transmembrane domain. However, cysteine residue 147 (huTR1 ORF numbering) may replace the deleted cysteine and thus the disulphide bridges are likely not affected. Therefore, TR1-3 is also a secreted form of huTR1 and functions as an agonist or an antagonist to huTR1 or other EGF family members, including EGF and TGF $\alpha$ . The determined cDNA sequence of TR1-3 is given in SEQ ID NO: 411 and the corresponding amino acid sequence is SEQ ID NO: 414.

TR1ɛ consists of the ORF of huTR1 minus amino acids 86 to 136. This deletion has the effect of deleting residues following the second cysteine of the EGF motif and the transmembrane domain. However, cysteine residue 147 (huTR1 ORF numbering) may replace the deleted cysteine and thus the disulphide bridges are likely not affected. Therefore, TR1ɛ is also a secreted form of huTR1 and functions as an agonist or an antagonist to huTR1 or other EGF family members, including EGF and TGFa. The determined cDNA sequence of TR1ɛ is given in SEQ ID NO: 371 and the corresponding polypeptide sequence in SEQ ID NO: 395.

TR1 $\phi$  consists of the ORF of huTR1 minus amino acids 36 to 44 and amino acids 95 to 136. These deletions have the effect of deleting part of the amino terminal linker sequence and the transmembrane domain. Therefore TR1 $\phi$  is a secreted form of huTR1 and binds with equal or greater affinity to the TR1 receptor as huTR1, since the EGF domain remains intact. It functions as an agonist or an antagonist to huTR1 or other EGF family members, including EGF and TGF $\alpha$ . The determined nucleotide sequence of TR1 $\phi$  is given in SEQ ID NO: 416 and the corresponding polypeptide sequence in SEQ ID NO: 417.

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#### Example 4

## IDENTIFICATION, ISOLATION AND CHARACTERIZATION OF DP3

A partial cDNA fragment, referred to as DP3, was identified by differential display RT-PCR (modified from Liang P and Pardee AB, Science 257:967-971, 1992) using mRNA from cultured rat dermal papilla and footpad fibroblast cells, isolated by standard cell biology techniques. This double stranded cDNA was labeled with [α<sup>32</sup>P]-dCTP and used to identify a full length DP3 clone by screening 400,000 pfu's of an oligo dT-primed rat dermal papilla cDNA library. The determined full-length cDNA sequence for DP3 is provided in SEQ ID NO: 119, with the corresponding amino acid sequence being provided in SEQ ID NO: 197. Plaque lifts, hybridization and screening were performed using standard molecular biology techniques.

# Example 5 ISOLATION AND CHARACTERIZATION OF KS1

#### Analysis of RNA transcripts by Northern Blotting

Northern analysis to determine the size and distribution of mRNA for muKS1 (SEQ ID NO: 263) was performed by probing murine tissue mRNA blots with a probe consisting of nucleotides 268-499 of muKS1, radioactively labeled with  $[\alpha^{32}P]$ -dCTP. Prehybridization, hybridization, washing, and probe labeling were performed as

described in Sambrook, et al., Ibid. mRNA for muKS1 was 1.6 kb in size and was observed to be most abundant in brain, lung, or any muscle, and heart. Expression could also be detected in lower intestine, skin, bone marrow, and kidney. No detectable signal was found in testis, spleen, liver, thymus, stomach.

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#### Human homologue of muKS1

MuKS1 (SEQ ID NO: 263) was used to search the EMBL database (Release 50, plus updates to June, 1998) to identify human EST homologues. The top three homologies were to the following ESTs: accession numbers AA643952, HS1301003 and AA865643. These showed 92.63% identity over 285 nucleotides, 93.64% over 283 nucleotides and 94.035% over 285 nucleotides, respectively. Frame shifts were identified in AA643952 and HS1301003 when translated. Combination of all three ESTs identified huKS1 (SEQ ID NO: 270) and translated polypeptide SEQ ID NO: 344. Alignment of muKS1 and huKS1 polypeptides indicated 95% identity over 96 amino acids.

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## Identification of KSCL009274 cDNA sequence

A directionally cloned cDNA library was constructed from immature murine keratinocytes and submitted for high-throughput sequencing. Sequence data from a clone designated KDCL009274 showed 35% identity over 72 amino acids with rat macrophage inflammatory protein-2B (MIP-2B) and 32% identity over 72 amino acids with its murine homologue. The insert of 1633bp (SEQ ID NO: 464; Fig. 15A) contained an open reading frame of 300bp with a 5' untranslated region of 202bp and a 3' untranslated region of 1161bp. A poly-adenylation signal of AATAAA is present 19 base pairs upstream of the poly-A tail. The mature polypeptide (SEQ ID NO: 465) is 77 amino acids in length containing 4 conserved cysteines with no ELR motif. The putative signal peptide cleavage site beween GLY 22 and Ser 23 was predicted by the hydrophobicity profile. This putative chemokine was identical to KS1. The full length sequence was screened against the EMBL database using the BLAST program and showed some identity at the nucleotide level with human EST clones AA643952, AA865643, and

HS1301003, respectively. A recently described human CXC chemokine, BRAK, has some identity with KS1 at the protein level. The alignment of KS1 (referred to in Fig. 15B as KLF-1), BRAK, and other murine  $\alpha$ -chemokines is shown in Fig. 15B. The phylogenetic relationship between KS1 and other  $\alpha$ -chemokine family members was determiend using the Phylip program. KS1 and BRAK demonstrate a high degree of divergence from the other  $\alpha$ -chemokines, supporting the relatively low homology shown in the multiple alignment.

## Bacterial expression and purification of muKS1 and huKS1

Polynucleotides 269-502 of muKS1 (SEQ ID NO: 271), encoding amino acids 23-99 of polypeptide muKS1 (SEQ ID NO: 345), and polynucleotides 55-288 of huKS1 (SEQ ID NO: 272), encoding amino acids 19-95 of polypeptide huKS1 (SEQ ID NO: 346), were cloned into the bacterial expression vector pET-16b (Novagen, Madison, Wisconsin), which contains a bacterial leader sequence and N-terminal 6xHistidine tag. These constructs were transformed into competent XL1-Blue *E. coli* as described in Sambrook et al., *Ibid*.

Starter cultures of recombinant BL 21 (DE3) *E. coli* (Novagen) containing SEQ ID NO: 271 (muKS1a) and SEQ ID NO: 272 (huKS1a) were grown in NZY broth containing 100 µg/ml ampicillin (Gibco-BRL Life Technologies) at 37°C. Cultures were spun down and used to inoculate 800 ml of NZY broth and 100 µg/ml ampicillin. Cultures were grown until the OD<sub>595</sub> of the cells was between 0.4 and 0.8. Bacterial expression was induced for 3 hours with 1 mM IPTG. Bacterial expression produced an induced band of approximately 15kDa for muKS1a and huKS1a.

MuKS1a and huKS1a were expressed in insoluble inclusion bodies. In order to purify the polypeptides, bacterial cell pellets were re-suspended in lysis buffer (20 mM Tris-HCl pH 8.0, 10 mM βMercaptoethanol, 1 mM PMSF). To the lysed cells, 1% NP-40 was added and the mix incubated on ice for 10 minutes. Lysates were further disrupted by sonication on ice at 95 W for 4 x 15 seconds and then centrifuged for 10 minutes at 18,000 rpm to pellet the inclusion bodies.

The pellet containing the inclusion bodies was re-suspended in lysis buffer containing 0.5% w/v CHAPS and sonicated for 5-10 seconds. This mix was stored on ice for 1 hour, centrifuged at 14000 rpm for 15 minutes at 4°C and the supernatant discarded. The pellet was once more re-suspended in lysis buffer containing 0.5% w/v CHAPS, sonicated, centrifuged, and the supernatant removed as before. The pellet was resuspended in solubilizing buffer (6 M guanidine HCl, 0.5 M NaCl, 20 mM Tris-HCl pH 8.0), sonicated at 95W for 4 x 15 seconds and centrifuged for 10 minutes at 18000 rpm and 4°C to remove debris. The supernatant was stored at 4°C. MuKS1a and huKS1a were purified by virtue of the N-terminal 6x histidine tag contained within the bacterial leader sequence, using a Nickel-Chelating sepharose column (Amersham Pharmacia, Uppsala, Sweden) and following the manufacturer's protocol. Proteins were purified twice over the column to reduce endotoxin contamination. In order to re-fold the proteins once purified, the protein solution was dialysed in a 4 M-2 M urea gradient in 20 mM tris-HCl pH 7.5 + 10% glycerol overnight at 4°C. The protein was then further dialysed 2x against 2 litres of 20 mM Tris-HCl pH 7.5 + 10% (w/v) glycerol. Preparations obtained were greater than 95% pure as determined by SDS-PAGE. Endotoxin contamination of purified proteins were determined using a limulus amebocyte lysate assay kit (BIO Whittaker, Walkersville, MD). Endotoxin levels were <0.1 ng/µg of protein. Internal amino acid sequencing was performed on tryptic peptides of KS1.

An Fc fusion protein was produced by expression in HEK 293 T cells. 35µg of KLF-1plGFc DNA to transfect 6 x 10<sup>6</sup> cells per flask, 200 mls of Fc containing supernatant was produced. The Fc fusion protein was isolated by chromatography using an Affiprep protein A resin (0.3 ml column, Biorad). After loading, the column was washed with 15 mls of PBS, followed by a 5 ml wash of 50 mM Na citrate pH 5.0. The protein was then eluted with 6 column volumes of 50 mM Na citrate pH 2.5, collecting 0.3 ml fractions in tubes containing 60µl of 2M Tris-HCI pH 8.0. Fractions were analyzed by SDS-PAGE.

Peptide sequencing of muKS1 and huKS1

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Bacterially expressed muKS1 and huKS1 were separated on polyacrylamide gels and induced bands of 15 kDa were identified. The predicted size of muKS1 is 9.4 kDa. To obtain the amino acid sequence of the 15 kDa bands, 20 µg recombinant muKS1 and huSK1 was resolved by SDS-PAGE and electroblotted onto Immobilon PVDF membrane (Millipore, Bedford, Massachusetts). Internal amino acid sequencing was performed on tryptic peptides of muKS1 and huKS1 by the Protein Sequencing Unit at the University of Auckland, New Zealand.

The determined amino acid sequences for muKS1 and huKS1 are given in SEQ ID NOS: 397 and 398, respectively. These amino acid sequences confirmed that the determined sequences are identical to those established on the basis of the cDNA sequences. The size discrepancy has previously been reported for other chemokines (Richmond A, Balentien E, Thomas HG, Flaggs G, Barton DE, Spiess J, Bordoni R, Francke U, Derynck R, "Molecular characterization and chromosomal mapping of melanoma growth stimulatory activity, a growth factor structurally related to beta-thromboglobulin," *EMBO J.* 7:2025-2033, 1988; Liao F, Rabin RL, Yannelli JR, Koniaris LG, Vanguri P, Farber JM, "Human Nig chemokine: biochemical and functional characterization," *J. Exp. Med.* 182:1301-1314, 1995). The isoelectric focusing point of these proteins was predicted to be 10.26 using DNASIS (HITACHI Software Engineering, San Francisco, California). Recombinant Fc tagged KS1 expresssed and purified using protein A affinity column chromatography revealed a homogenous protein with a molecular mass of 42kDa.

### Oxidative burst assay

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Oxidative burst assays were used to determine responding cell types. 1 x 10<sup>7</sup> PBMC cells were resuspended in 5 ml HBSS, 20mM HEPES, 0.5% BSA and incubated for 30 minutes at 37°C with 5 µl 5 mM dichloro-dihydrofluorescein diacetate (H<sub>2</sub>DCFDA, Molecular Probes, Eugene, Oregon). 2 x 10<sup>5</sup> H<sub>2</sub>DCFDA-labeled cells were loaded in each well of a flat-bottomed 96 well plate. 10 µl of each agonist was added simultaneously into the well of the flat-bottomed plate to give final concentrations of 100 ng/ml (fMLP was used at 10 µM). The plate was then read on a Victor<sup>2</sup> 1420

multilabel counter (Wallac, Turku, Finland) with a 485 nm excitation wavelength and 535 nm emission wavelength. Relative fluorescence was measured at 5 minute intervals over 60 minutes.

A pronounced respiratory burst was identified in PBMC with a 2.5 fold difference between control treated cells (TR1) and cells treated with 100 ng/ml muKS1 (Fig. 8). Human stromal derived factor-1α (SDF1α) (100 ng/ml) and 10 μM formyl-Met-Leu-Phe (fMLP) were used as positive controls.

#### Chemotaxis assay

Cell migration in response to muKS1 was tested using a 48 well Boyden's chamber (Neuro Probe Inc., Cabin John, Maryland) as described in the manufacturer's protocol. In brief, agonists were diluted in HBSS, 20mM HEPES, 0.5% BSA and added to the bottom wells of the chemotactic chamber. THP-1 cells were re-suspended in the same buffer at 3 x 10<sup>5</sup> cells per 50 µ1. Top and bottom wells were separated by a PVP-free polycarbonate filter with a 5 µm pore size for monocytes or 3 µm pore size for lymphocytes. Cells were added to the top well and the chamber incubated for 2 hours for monocytes and 4 hours for lymphocytes in a 5% CO<sub>2</sub> humidified incubator at 37°C. After incubation, the filter was fixed and cells scraped from the upper surface. The filter was then stained with Diff-Quick (Dade International Inc., Miami, Florida) and the number of migrating cells counted in five randomly selected high power fields. The results are expressed as a migration index (the number of test migrated cells divided by the number of control migrated cells).

Using this assay, muKS1 was tested against T cells and THP-1 cells. MuKS1 induced a titrateable chemotactic effect on THP-1 cells from 0.01 ng/ml to 100 ng/ml (Fig. 9). Human SDF1α was used as a positive control and gave an equivalent migration. MuKS1 was also tested against IL-2 activated T cells. However, no migration was evidence for muKS1 even at high concentrations, whereas SDF-1α provided an obvious titrateable chemotactic stimulus. Therefore, muKS1 appears to be chemotactic for THP-1 cells but not for IL-2 activated T cells at the concentrations tested.

#### Flow cytometric binding studies

Binding of KLF-1 to THP-1 and Jurkat cells was tested in the following manner. THP-1 or Jurkat cells (5 x 106) were resuspended in 3 mls of wash buffer (2% FBS and 0.2% sodium azide in PBS) and pelleted at 4°C, 200 x g for 5 minutes. Cells were then blocked with 0.5% mouse and goat sera for 30 minutes on ice. Cells were washed, pelleted, resuspended in 50 µl of KLF-1Fc at 10 µg/ml and incubated for 30 minutes on ice. After incubation, the cells were prepared as before and resuspended in 50 µl of goat anti-human IgG biotin (Southern Biotechnology Associates, AL) at 10 µg/ml and incuated for 30 minutes on ice. Finally, cells were washed, pelleted and resuspended in 50 μl of streptavidin-RPE (Southern Biotechnology Associates, AL) at 10 μg/ml and incuabated for a further 30 minutes on ice in the dark. Cells were washed and resuspended in 250 µl of wash buffer and stained with 1µl of 10 µg/ml propidium iodide (Sigma) to exclude any dead cells. Purified Fc fragment (10 µg/ml) was used as a negative control in place of KLF-1Fc to determine non-specific binding. Ten thousand gated events were analyzed on log scale using PE filter arrangement with peak transmittance at 575 nm and bandwidth of 10 nm on an Elite cell sorter (Coulter Cytometry).

The respiratory burst and migration assays indicated that KS1 is active on monocytes and not T cells; therefore, the KS1 Fc fusion protein was tested in a binding study with THP-1 and Jurkat T cells. KS1 Fc showed a marked positive shift on THP-1 cells compared with the Fc fragment alone. In contrast, KS1 demonstrated no positive binding with Jurkat cells in an identical experiment.

#### 25 Full length sequence of muKS1 clone

The nucleotide sequence of muKS1 was extended by determining the base sequence of additional ESTs. Combination of all the ESTs identified the full-length muKS1 (SEQ ID NO: 370) and the corresponding translated polypeptide sequence in SEQ ID NO: 394.

## Analysis of human RNA transcripts by Northern blotting

Northern blot analysis to determine the size and distribution of mRNA for the human homologue of muKS1 was performed by probing human tissue blots (Clontech, Palo Alto, California) with a radioactively labeled probe consisting of nucleotides 1 to 288 of huKS1 (SEQ ID NO: 270). Prehybridization, hybridization, washing, and probe labeling were performed as described in Sambrook, et al., Ibid. mRNA for huKS1 was 1.6 kb in size and was observed to be most abundance in kidney, liver, colon, small intestine, and spleen. Expression could also be detected in pancreas, skeletal muscle, placenta, brain, heart, prostate, and thymus. No detectable signal was found in lung, ovary, and testis.

## Analysis of human RNA transcripts in tumor tissue by Northern blotting

Northern blot analysis to determine distribution of huKS1 in cancer tissue was performed as described previously by probing tumor panel blots (Invitrogen, Carlsbad, California). These blots make a direct comparison between normal and tumor tissue. MRNA was observed in normal uterine and cervical tissue but not in the respective tumor tissue. In contrast, expression was up-regulated in breast tumor and down-regulated in normal breast tissue. No detectable signal was found in either overy or ovarian tumors.

## Injection of bacterially recombinant muKS1 into C3H/HeJ mice

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Eighteen C3H/HeJ mice were divided into 3 groups and injected intraperitioneally with muKS1, GV14B, or phosphate buffered saline (PBS). GV14B is a bacterially expressed recombinant protein used as a negative control. Group 1 mice were injected with 50 μg of muKS1 in 1 ml of PBS; Group 2 mice were injected with 50 μg of GV14B in 1 ml of PBS; and Group 3 mice with 1 ml of PBS. After 18 hours, the cells in the peritoneal cavity of the mice were isolated by intraperitoneal lavage with 2 x 4 ml washes with harvest solution (0.02% EDTA in PBS). Viable cells were counted from individual

mice from each group. Mice injected with 50 µg of muKS1 had on average a 3-fold increase in cell numbers (Fig. 10).

20 µg of bacterial recombinant muKS1 was injected subcutaneously into the left hind foot of three C3H/HeJ mice. The same volume of PBS was injected into the same site on the right-hand side of the same animal. After 18 hours, mice were examined for inflammation. All mice showed a red swelling in the foot pad injected with bacterially recombinant KS1. From histology, sites injected with muKS1 had an inflammatory response of a mixed phenotype with mononuclear and polymorphonuclear cells present.

#### 10 Injection of bacterially expressed muKSla into nude mice

To determine whether T cells are required for the inflammatory response, the experiment was repeated using nude mice. Two nude mice were anaesthetised intraperitoneally with 75 µl of 1/10 dilution of Hypnorm (Janssen Pharmaceuticals, Buckinghamshire, England) in phosphate buffered saline. 20ug of bacterially expressed muKS1a (SEQ ID NO: 345) was injected subcutaneously in the left hind foot, ear and left-hand side of the back. The same volume of phosphate buffered saline was injected in the same sites but on the right-hand side of the same animal. Mice were left for 18 hours and then examined for inflammation. Both mice showed a red swelling in the ear and foot sites injected with the bacterially expressed protein. No obvious inflammation could be identified in either back site. Mice were culled and biopsies taken from the ear, back and foot sites and fixed in 3.7% formol saline. Biopsies were embedded, sectioned and stained with Haemotoxylin and eosin. Sites injected with muKS1a had a marked increase in polymorphonuclear granulocytes, whereas sites injected with phosphate buffered saline had a low background infiltrate of polymorphonuclear granulocytes.

<u>Discussion</u>

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Chemokines are a large superfamily of highly basic secreted proteins with a broad number of functions (Baggiolini, et al., Annu. Rev. Immunol., 15:675-705, 1997; Ward, et al., Immunity, 9:1-11, 1998; Horuk, Nature, 393:524-525, 1998). The polypeptide

sequences of muKS1 and huKS1 have similarity to CXC chemokines, suggesting that this protein will act like other CXC chemokines. The in vivo data from nude mice supports this hypothesis. This chemokine-like protein may therefore be expected to stimulate leukocyte, epithelial, stromal, and neuronal cell migration; promote angiogenesis and vascular development; promote neuronal patterning, hemopoietic stem cell mobilization, keratinocyte and epithelial stem cell patterning and development, activation and proliferation of leukocytes; and promotion of migration in wound healing events. It has recently been shown that receptors to chemokines act as co-receptors for HIV-1 infection of CD4+ cells (Cairns, et al., Nature Medicine, 4:563-568, 1998) and that high circulating levels of chemokines can render a degree of immunity to those exposed to the HIV virus (Zagury, et al., Proc. Natl. Acad. Sci. USA 95:3857-3861, 1998). This novel gene and its encoded protein may thus be usefully employed as regulators of epithelial, lymphoid, myeloid, stromal, and neuronal cells migration and cancers; as agents for the treatment of cancers, neuro-degenerative diseases, inflammatory autoimmune diseases such as psoriasis, asthma and Crohn's disease for use in wound healing; and as agents for the prevention of HIV-1 binding and infection of leukocytes.

We have also shown that muKS1 promotes a quantifiable increase in cell numbers in the peritoneal cavity of C3H/HeJ mice injected with muKS1. Furthermore, we have shown that muKS1 induces an oxidative burst in human peripheral blood mononuclear cells and migration in the human monocyte leukemia cell line, THP-1, suggesting that monocyte/macrophages are one of the responsive cell types for KS1. In addition to this, we demonstrated that huKS1 was expressed at high levels in a number of non-lymphoid tissues, such as the colon and small intestine, and in breast tumors. It was also expressed in normal uterine and cervical tissue, but was completely down-regulated in their respective tumors. It has recently been shown that non-ELR chemokines have demonstrated angiostatic properties. IP-10 and Mig, two non-ELR chemokines, have previously been shown to be up-regulated during regression of tumors (Tannenbaum CS, Tubbs R, Armstrong D, Finke JH, Bukowski RM, Hamilton TA, "The CXC Chemokines IP-10 and Mig are necessary for IL-12-mediated regression of the mouse RENCA

tumor," J. Immunol. 161: 927-932, 1998), with levels of expression inversely correlating with tumor size (Kanegane C, Sgadari C, Kanegane H, Teruya-Feldstine J, Yao O, Gupta G, Farber JM, Liao F, Liu L, Tosato G, "Contribution of the CXC Chemokines IP-10 and Mig to the antitumor effects of IL-12," J. Leuko. Biol. 64: 384-392, 1998). Furthermore, neutralizing antibodies to IP-10 and Mig would reduce the anti-tumor effect, indicating the contribution these molecules make to the anti-tumor effects. Therefore, it is expected that in the case of cervical and uterine tumors, KS1 would have similar properties.

The data demonstrates that KS1 is involved in cell migration showing that one of the responsive cell types is monocyte/macrophage. The human expression data in conjunction with the *in vitro* and *in vivo* biology demonstrates that this molecule may be a useful regulator in cell migration, and as an agent for the treatment of inflammatory diseases, such as Crohn's disease, ulcerative colitis, and rheumatoid arthritis; and cancers, such as cervical adenocarcinoma, uterine leiomyoma, and breast invasive ductal carcinoma.

## Example 6

## CHARACTERIZATION OF KS2

KS2 contains a transmembrane domain and may function as either a membranebound ligand or a receptor. Northern analysis indicated that the mRNA for KS2 was expressed in the mouse keratinocyte cell line, Pam212, consistent with the cDNA being identified in mouse keratinocytes.

#### Mammalian Expression

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To express KS2, the extracellular domain was fused to the amino terminus of the constant domain of immunoglobulinG (Fc) that had a C-terminal 6xHistidine tag. This was performed by cloning polynucleotides 20-664 of KS2 (SEQ ID NO: 273), encoding amino acids 1-215 of polypeptide KS2 (SEQ ID NO: 347), into the mammalian expression vector pcDNA3 (Invitrogen, NV Leek, Netherlands), to the amino terminus of

the constant domain of immunoglobulinG (Fc) that had a C-terminal 6xHistidine tag. This construct was transformed into competent XL1-Blue *E. coli* as described in Sambrook et al., *Ibid*. The Fc fusion construct of KS2a was expressed by transfecting Cos-1 cells in 5 x T175 flasks with 180 µg of KS1a using DEAE-dextran. The supernatant was harvested after seven days and passed over a Ni-NTA column. Bound KS2a was eluted from the column and dialysed against PBS.

The ability of the Fc fusion polypeptide of KS2a to inhibit the IL-2 induced growth of concanavalin A stimulated murine splenocytes was determined as follows. A single cell suspension was prepared from the spleens of BALB/c mice and washed into DMEM (GIBCO-BRL) supplemented with 2 mM L-glutamine, 1 mM sodium pyruvate, 0.77 mM L-asparagine, 0.2 mM L-arganine, 160 mM penicillin G, 70 mM dihydrostreptomycin sulfate, 5 x 10<sup>-2</sup> mM beta mercaptoethanol and 5% FCS (cDMEM). Splenocytes (4 x  $10^6$ /ml) were stimulated with 2  $\mu$ g/ml concanavalin A for 24 hrs at 37°C in 10% CO2. The cells were harvested from the culture, washed 3 times in cDMEM and resuspended in cDMEM supplemented with 10 ng/ml rhuIL-2 at 1 x 10<sup>5</sup> cells/ml. The assay was performed in 96 well round bottomed plates in 0.2 ml cDMEM. The Fc fusion polypeptide of KS2a, PBS, LPS and BSA were titrated into the plates and 1 x 10<sup>4</sup> activated T cells (0.1 ml) were added to each well. The plates were incubated for 2 days in an atmosphere containing 10% CO<sub>2</sub> at 37°C. The degree of proliferation was determined by pulsing the cells with 0.25 uCi/ml tritiated thymidine for the final 4 hrs of culture after which the cells were harvested onto glass fiber filtermats and the degree of thymidine incorporation determined by standard liquid scintillation techniques. As shown in Fig. 6, the Fc fusion polypeptide of KS2a was found to inhibit the IL-2 induced growth of concanavalin A stimulated murine splenocytes, whereas the negative controls PBS, BSA and LPS did not.

This data demonstrates that KS2 is expressed in skin keratinocytes and inhibits the growth of cytokine induced splenocytes. This indicates a role for KS2 in the regulation of skin inflammation and malignancy.

#### Example 7

### Characterization of KS3

KS3 encodes a polypeptide of 40 amino acids (SEQ ID NO: 129). KS3 contains a signal sequence of 23 amino acids that would result in a mature polypeptide of 17 amino acids (SEQ ID NO: 348; referred to as KS3a).

KS3a was prepared synthetically (Chiron Technologies, Victoria, Australia) and observed to enhance transferrin-induced growth of the rat intestinal epithelial cells IEC-18 cells. The assay was performed in 96 well flat-bottomed plates in 0.1 ml DMEM (GIBCO-BRL Life Technologies) supplemented with 0.2% FCS. KS3a (SEQ ID NO: 348), apo-Transferrin, media and PBS-BSA were titrated either alone, with 750 ng/ml Apo-transferrin or with 750 ng/ml BSA, into the plates and 1 x10<sup>3</sup> IEC-18 cells were added to each well. The plates were incubated for 5 days at 37°C in an atmosphere containing 10% CO<sub>2</sub>. The degree of cell growth was determined by MTT dye reduction as described previously (*J. Imm. Meth.* 93:157-165, 1986). As shown in Fig. 7, KS3a plus Apo-transferrin was found to enhance transferrin-induced growth of IEC-18 cells, whereas KS3a alone or PBS-BSA did not, indicating that KS3a and Apo-transferrin act synergistically to induce the growth of IEC-18 cells.

This data indicates that KS3 is epithelial derived and stimulates the growth of epithelial cells of the intestine. This suggests a role for KS3 in wound healing, protection from radiation- or drug-induced intestinal disease, and integrity of the epithelium of the intestine.

SEQ ID NOS: 1-725 are set out in the attached Sequence Listing. The codes for polynucleotide and polypeptide sequences used in the attached Sequence Listing confirm to WIPO Standard ST.25 (1988), Appendix 2.

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All references cited herein, including patent references and non-patent references, are hereby incorporated by reference in their entireties.

Although the present invention has been described in terms of specific embodiments, changes and modifications can be carried out without departing from the

scope of the invention which is intended to be limited only by the scope of the appended claims.

#### We claim:

- 1. An isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of: (a) sequences recited in SEQ ID NOS: 466-487, 510, 511 and 514-623; (b) complements of the sequences recited in SEQ ID NOS: 466-487, 510, 511 and 514-623; (c) reverse complements of the sequences recited in SEQ ID NOS: 466-487, 510, 511 and 514-623; (d) reverse sequences of the sequences recited in SEQ ID NOS: 466-487, 510, 511 and 514-623; (e) sequences having at least a 99% probability of being the same as a sequence selected from any of the sequences in (a)-(d), above, as measured by the computer algorithm BLASTP using the running parameters described above; (f) nucleotide sequences having at least 75% identity to any of the sequences in (a)-(d), above, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (g) nucleotide sequences having at least 90% identity to any of the sequences in (a)-(d), above, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (h) nucleotide sequences having at least 95% identity to any of the sequences in (a)-(d), above, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; and (g) open reading frames of SEQ ID NOS: 1-119, 198-276, 349-372, 399-405, 410-412, 416, 418-455, 464, 466-487, 510, 511 and 514-623.
  - 2. An expression vector comprising an isolated polynucleotide of claim 1.
  - 3. A host cell transformed with an expression vector of claim 2.
- 4. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of: (a) sequences provided in SEQ ID NOS: 488-509, 512, 513 and 624-725; (b) sequences having at least a 99% probability of being the same as a sequence of SEQ ID NOS: 488-509, 512, 513 and 624-725, as measured by the computer algorithm BLASTP using the running parameters described above; (c) sequences having

at least 75% identity to a sequence provided in SEQ ID NOS: 488-509, 512, 513 and 624-725, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (d) sequences having at least 90% identity to a sequence provided in SEQ ID NOS: 488-509, 512, 513 and 624-725, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (e) sequences having at least 95% identity to a sequence provided in SEQ ID NOS: 488-509, 512, 513 and 624-725, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; and (f) sequences encoded by a sequence provided in SEQ ID NOS: 488-509, 512, 513 and 624-725.

- 5. An isolated polynucleotide encoding a polypeptide of claim 4.
- 6. An expression vector comprising an isolated polynucleotide of claim 5.
- 7. A host cell transformed with an expression vector of claim 6.
- 8. An isolated polypeptide comprising at least a functional portion of a polypeptide having an amino acid sequence selected from the group consisting of: (a) sequences provided in SEQ ID NOS: 196, 488-509, 512, 513 and 624-725; (b) sequences having at least a 99% probability of being the same as a sequence of SEQ ID NOS: 196, 488-509, 512, 513 and 624-725, as measured by the computer algorithm BLASTP using the running parameters described above; (c) sequences having at least 75% identity to a sequence provided in SEQ ID NOS: 196, 488-509, 512, 513 and 624-725, as measured by the computer algorithm BLASTP, using the running parameters and identity test defined above; (d) sequences having at least 90% identity to a sequence provided in SEQ ID NOS: 196, 488-509, 512, 513 and 624-725, as measured by the computer algorithm BLASTP, using the running parameters and identity test defined above; (e) sequences having at least 95% identity to a sequence provided in SEQ ID

NOS: 196, 488-509, 512, 513 and 624-725, as measured by the computer algorithm BLASTP, using the running parameters and identity test defined above; and (f) sequences encoded by a sequence provided in SEQ ID NOS: 466-487, 510, 511 and 514-623.

- A method for stimulating keratinocyte growth and motility in a patient, comprising administering to the patient a composition comprising a polypeptide of claim
- 10. The method of claim 9, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: (a) SEQ ID NOS: 187, 196, 342, 343, 395, 397 and 398; (b) sequences having at least about 50% identity to a sequence of SEQ ID NOS: 187, 196, 342, 343, 395, 397 and 398 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (c) sequences having at least about 75% identity to a sequence of SEQ ID NOS: 187, 196, 342, 343, 395, 397 and 398 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (d) sequences having at least about 90% identity to a sequence of SEQ ID NOS: 187, 196, 342, 343, 395, 397 and 398 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; and (e) sequences comprising amino acids 54-104 of SEQ ID NO: 196.
- 11. A method for inhibiting the growth of cancer cells in a patient, comprising administering to the patient a composition comprising a polypeptide of claim 4.
- 12. The method of claim 11, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: (a) SEQ ID NOS: 187, 196, 342, 343, 397 and 398; (b) sequences having at least 75% identity to a sequence of SEQ ID NOS: 187, 196, 342, 343, 397 and 398, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (c) sequences having at least 90%

identity to a sequence of SEQ ID NOS: 187, 196, 342, 343, 397 and 398, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (d) sequences having at least 95% identity to a sequence of SEQ ID NOS: 187, 196, 342, 343, 397 and 398, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; and (e) sequences comprising amino acids 54-104 of SEQ ID NO: 196.

- 13. A method for modulating angiogenesis in a patient, comprising administering to the patient a composition comprising a polypeptide of claim 4.
- 14. The method of claim 13, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: (a) SEQ ID NOS: 187, 196, 342, 343, 397 and 398; (b) sequences having at least 75% identity to a sequence of SEQ ID NOS: 187, 196, 342, 343, 397 and 398 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (c) sequences having at least 90% identity to a sequence of SEQ ID NOS: 187, 196, 342, 343, 397 and 398 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (d) sequences having at least 95% identity to a sequence of SEQ ID NOS: 187, 196, 342, 343, 397 and 398 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; and (e) sequences comprising amino acids 54-104 of SEQ ID NO: 196..
- 15. A method for inhibiting angiogenesis and vascularization of tumors in a patient, comprising administering to a patient a composition comprising a polypeptide of claim 4.
- 16. The method of claim 15, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: (a) SEQ ID NOS: 187, 196, 342, 343, 397 and 398; (b) sequences having at least 75% identity to a sequence of SEQ ID NOS:

187, 196, 340, 342-346, 397 and 398, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (c) sequences having at least 90% identity to a sequence of SEQ ID NOS: 187, 196, 340, 342-346, 397 and 398, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (d) sequences having at least 95% identity to a sequence of SEQ ID NOS: 187, 196, 340, 342-346, 397 and 398, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; and (e) sequences comprising amino acids 54-104 of SEQ ID NO: 196.

- 17. A method for modulating skin inflammation in a patient, comprising administering to the patient a composition comprising a polypeptide of claim 4.
- 18. The method of claim 17, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: (a) SEQ ID NOS: 338 and 347; and (b) sequences having at least 75% identity to a sequence of SEQ ID NOS: 338 and 347 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (c) sequences having at least 90% identity to a sequence of SEQ ID NOS: 338 and 347 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; and (d) sequences having at least 95% identity to a sequence of SEQ ID NOS: 338 and 347 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above. \( \)
- 19. A method for stimulating the growth of epithelial cells in a patient, comprising administering to the patient a composition comprising a polypeptide of claim 4.
- 20. The method of claim 19, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: (a) SEQ ID NOS: 129 and 348; (b) sequences having at least 75% identity to a sequence of SEQ ID NOS: 129 and 348 as measured by the computer algorithm BLASTP using the running parameters and identity

test defined above; (c) sequences having at least 90% identity to a sequence of SEQ ID NOS: 129 and 348 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; and (d) sequences having at least 95% identity to a sequence of SEQ ID NOS: 129 and 348 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above.

- 21. A method for inhibiting the binding of HIV-1 to leukocytes in a patient, comprising administering to the patient a composition comprising a polypeptide of claim 4.
- 22. The method of claim 21, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: (a) SEQ ID NOS: 340, 344, 345, 346 and 465; (b) sequences having at least 75% identity to a sequence of SEQ ID NOS: 340, 344, 345, 346 and 465 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (c) sequences having at least 90% identity to a sequence of SEQ ID NOS: 340, 344, 345, 346 and 465 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; and (d) sequences having at least 95% identity to a sequence of SEQ ID NOS: 340, 344, 345, 346 and 465 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above.
- 23. A method for treating an inflammatory disease in a patient, comprising administering to the patient a composition comprising a polypeptide of claim 4.
- 24. The method of claim 23, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: (a) SEQ ID NOS: 340, 344, 345, 346 and 465; (b) sequences having at least 75% identity to a sequence of SEQ ID NOS: 340, 344, 345, 346 and 465 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (c) sequences having at least 90%

identity to a sequence of SEQ ID NOS: 340, 344, 345, 346 and 465 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; and (d) sequences having at least 95% identity to a sequence of SEQ ID NOS: 340, 344, 345, 346 and 465 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above.

- 25. A method for treating cancer in a patient, comprising administering to the patient a composition comprising a polypeptide of claim 4.
- 26. The method of claim 25, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: (a) SEQ ID NOS: 340, 344, 345, 346 and 465; (b) sequences having at least 75% identity to a sequence of SEQ ID NOS: 340, 344, 345, 346 and 465 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (c) sequences having at least 90% identity to a sequence of SEQ ID NOS: 340, 344, 345, 346 and 465 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; and (d) sequences having at least 95% identity to a sequence of SEQ ID NOS: 340, 344, 345, 346 and 465 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above.
- 27. A method for treating a neurological disease in a patient, comprising administering to the patient a composition comprising a polypeptide of claim 4.
- 28. The method of claim 27, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: (a) SEQ ID NOS: 187, 196, 340, 342-346, 397 and 398; (b) sequences having at least 75% identity to a sequence of SEQ ID NOS: 187, 196, 340, 342-346, 397 and 398, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (c) sequences having at least 90% identity to a sequence of SEQ ID NOS: 187, 196, 340, 342-346, 397

and 398, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (d) sequences having at least 95% identity to a sequence of SEQ ID NOS: 187, 196, 340, 342-346, 397 and 398, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; and (e) sequences comprising amino acids 54-104 of SEQ ID NO: 196.

#### SEQUENCE LISTING

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Watson, James D. Strachan, Lorna Sleeman, Matthew Onrust, Rene Murison, James G. Kumble, Krishanand D.

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aagaagtacc agetgaacct gecatettac cetgacacag agtgtgteta eegtetacag
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aaaaaaaaa aaactcg
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tggttaggag cetggetagg tatetttgag agatggatge agetggetae teaggeaggt
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ataagacaaa ttatatattg ctatgaagct cttcttacca gggtcagttt ttacatttta
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766
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     <212> DNA
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962
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ctaatataga ttatttatga attcaggtgg cttaatggta tatgcatgaa ttagtagtaa
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aacaagaact agggccagca agtggcttaa gggtgcctgc taaccatctc agccacctga
gttcagtctc caggaaccac acagtg
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      <212> DNA
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      <221> unsure
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      <221> unsure
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1140

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PCT/NZ01/00099 WO 01/90357

960

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 cttectatte tttecegtet ttagggeete etcacagtgt tgttttetaa caacgeagge
                                                                       120
 atgagaagge acteactgtg tgctccctca ggcctggcct ctcctggtga ttgtcttctt
                                                                       180
                                                                       204
 cetetgtgte etetteatec caat
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       <211> 300
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     · <220>
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tatttatgac ttgggttaag ggagtttgct gtgcaatcat gaagaccaga gttcagatcc
                                                                       ′60
cagcacccat atagcaagag agcatacaag aagcacctgt gactgcactc tgaagaatcc
                                                                      120
aacacettet tetggeetee atggeacaca gaacececca acacatgete atceactete
                                                                      1806
                                                                      240
aaagagacat acataaaaat aaatatttag gtcctgggtc cctcagagac tagtcttcac
                                                                      300
aggtectaaa tacaaacgna geggacegca aagggtgagg gagtggneet gaagaageta,
       <210> 80
       <211> 214
       <212> DNA
       <213> mouse
       <400> 80
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 aggtgaggaa acccaggaag cagggtcatg accccgcaga ggtcggggct cctggtgcag
                                                                        120
                                                                        180
 aggatcagat cttgtgtgac ttctgtcttg gggccagcag agtaagggca gtgaaatcct
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 gtctgacctg catggtgaaa tactgtaagg agca
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<210> 83 <211> 332 <212> DNA <213> mouse	
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<210> 85 <211> 273	

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       <213> mouse
       <220>
       <221> misc_feature
       <222> (1)...(273)
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cantececeg tecatectga agegggetee tegggagegt ceaggteang tggeetttaa
                                                                      180
eggeateane gtetactatt teccaeggtg ceaaggatte accagtgtge ceaageegtg
                                                                      240
gtggctgtac cctgggnatg gcttctcggc aca
       <210> 86
       <211> 218
       <212> DNA
       <213> mouse
       <400> 86
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                                                                       120
 ctecttetat aacegeetee aagagetgge cteaetgttg ecceggeegg ataageeetg
                                                                        180
 cccagcctat gtggagccta tgactgtggt ttgtcacc
                                                                       218
       <210> 87
       <211> 335
       <212> DNA
       <213> mouse
       <400> 87
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 getggeeggt ttectacaca geageacetg ceatggagee tggeeacaag gecacteaga
                                                                        120
 gctgggtgga cagagtgtga ccagaaactc cctgtgggtt ctgataaagg attctcccat
                                                                       180
 aggcaaggtt cagagaacct gggcctcctg ttctcaggga ggcctgtcta tccccagcct
                                                                        240
                                                                        300
 ctgagctgtt tcgtcctagt tggtgagtta agtggcatag ccctcttgag gcctctgatg
 tggaagggc acagaattgc aattattctt gcatg
                                                                        335
       <210> 88
       <211> 410
       <212> DNA
       <213> mouse
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                                                                        120
 accttggcaa tgtaacttgg gaggtteeca cacacccagg gctgtgcate gtgaaattet
                                                                       180
 gtotootgag acgotgagaa accottoott gcagotataa tgggcotggc cgcccagtgt
                                                                        240
 ggagctgtag cttcccacga cgtagccctc aggaacttca ggagggatgc cacagtctat
                                                                       300
 ttetgaaaac aaaaccgtgt caacttettt actttacaaa tgcaagtttt cagaatccac
                                                                        360
 catctctctg cacccatacc ccatgcctca caccccagac cctgtgttag
                                                                        410
       <210> 89
       <211> 279
       <212> DNA
       <213> mouse
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<220>

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<400> 89
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Cacacacaca cacacaca cacacacaca caccccaagg cttagagacc attgeagaag
                                                                 120
agaagagttt atgggaaatc ttggagaaaa cattggatgg tttgagagaa tggttaggag
                                                                 180
240
gacagggtgg agggcattgt ccgacagaac cattgctgt
                                                                 279
      <210> 90
      <211> 398
      <212> DNA
      <213> mouse
      <400> 90
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                                                                  60
gtggatgtac tgttttgagc cctgtgtgga acttctgaac ttcgtgctgt aactttcaga
                                                                 120
actettagae atgggtgtge teactgaact ctagggtetg tgtgetagat getgeeaacg
                                                                 180
ctgtattcag gacctgaagt gagtacccgt gtggatccag accaatccag tgtgagacta
                                                                 240
ctgaagaaca tctgttgcca gaacggccac accaaacaga tggagtgccc cagcacttag
cttcttaaat aacatcggaa ccattcagcc agcgagtctg tgtttgcttt ttgttaaatt
                                                                 360
gtccgccgaa tctaaattcc tccaaaaggc ttgtgacc
                                                                 398
      <210> 91
     <211> 279
      <212> DNA
      <213> mouse
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tggcgagaaa gcaagaccca gtggtagaca gattagcatt actgtacagc ttctttgggt
                                                                 120
gttcgaggaa gcccggctgg accatagtgg ccacggcggt gaggtaggcg tggacagggc
                                                                 180
tgaccagtcc aagttaagga cgttcgggtc catgttaacc ctgccttgta cgtccagcat
                                                                 240
cgtaagaaaa aacacttgag aacccgaaga ggagatgga
                                                                 279
     <210> 92
     <211> 401
     <212> DNA
     <213> mouse
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                                                                  60
120
cacgetetge aatgaateat gtggcacega gtetacgeca aggeeeega gaaaetttat
                                                                 180
tecatagatg ggcagatggt teccaaagtt acactacaga actacaaate gactettaaa
                                                                 240
attaaaacgg gactttacaa gcattctaga agactcaaac ttgaagcaat ttttggaaaa
                                                                 300
taaatgtaca gagaaaagat ettgaageta etgaacagag aaccetcatt aaccgagcaa
                                                                 360
atacatecta tggagettee gaggagtaca cagacagace g
                                                                 401
     <210> 93
     <211> 339
      <212> DNA
     <213> mouse
     <400> 93
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ccactgacct teccagaagg tgacageegg eggeggatgt tgtcaaggag eegagatagt ccageagtge eteggtacce agaagaeggg etgteteece ecaaaagaeg gegacatteg atgagaagte accacagtga teteacattt tgegagatta tectgatgga gatgaggtee catgatgeag eetggeettt eetagageet gtgaaceete gettggtgag tggatacega eggtgteatea agaaceetat ggattttee accatgegag aaegeetget eegtggaggg tacactaget cagaagagtt tgeagetgat getetgetg	120 180 240 300 339
<210> 94 <211> 55 <212> DNA <213> mouse <400> 94	
ggggtgtggg caacttggat aacctcagct gcttccatct ggctgacatc tttgg  <210> 95  <211> 186  <212> DNA  <213> mouse  <400> 95	
ggactetgge tteetgggge tgeggeegae eteggtggat eeegetetga ggeggeggeg geggggeece agaaacaaga agegeggetg gaggaggete geegaggage egetggggtt agaggtegae eagtteetgg aagaegteeg getacaggag egeaegaeeg gtggettgtt ggeaga	60 120 180 186
<210> 96 <211> 244 <212> DNA <213> mouse	
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<210> 97 <211> 116 <212> DNA <213> mouse	, • es.
<220> <221> unsure <222> (11)(11)	•
<221> unsure <222> (13)(13) <221> unsure <222> (41)(41)	
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       <211> 307
       <212> DNA
       <213> mouse
       <400> 98
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                                                                            60
 cgaattcatg acacctgtga tccaggacaa cccctcaggc tggggtccct gtgccgttcc
                                                                           120
 tgagcaattt cgggatatgc cctaccagcc attcagcaaa ggagatcggc tgggaaaggt
                                                                           180
 tgcagactgg acaggggcca cataccagga caagaggtac acaaacaagt attcctctca
                                                                           240
 gttcggtggg gggagtcagt atgcatattt ccatgaggag gatgagacaa gctttccagc
                                                                           .300
 tgggtgg
                                                                           307
       <210> 99
    . <211> 360
       <212> DNA
       <213> mouse
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       <221> misc_feature
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       <223> n = A,T,C or G
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tgtcccagca gaatccagtg acaggaagga gtttctgagg caggggagga ggcttctcca
                                                                          120
tgggaaccag acagccttg ttcactgtat aagtgccctg atcacagca gaatgaagtg
ccaggttgct cagaagcaca aagggtgtgg ctactggcc taaccatgga ctacgtggtt
                                                                          180
                                                                          240
ctaaccaaag actctagaac tetggggtgg gggagaaaca atgtgttetg tgetecagaa
                                                                          300
ccttnggctt cctggcccat atggatgggc ttggcaagga acctacctct tctctaaggt
                                                                          360
       <210> 100
       <211> 257
       <212> DNA
       <213> mouse
       <400> 100
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 gggtggggtg ggaggggggg gagccaccgc taccgccgcc gcctcccggg tgggcgcct
                                                                           120
                                                                           180 ·
 teteettaga egeeggegae eeaggaegag ggetteatea etgtaaatgg ttgeaageeg
 acaaagctgc acctcctgaa aaagacggac agcccatcgc gtgagctgta gaaatttgtg
                                                                           240
 gacgcatttc tatcggt ·
                                                                           25%
       <210> 101
       <211> 203
       <212> DNA
       <213> mouse
       <400> 101
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 gcatcctcaa gaggcccacc agcaacggtg tggtcagcag ccccaactcc accagcaggc
                                                                           120
 cagocottco tgtcaagtco ctagcacago gggaggcaga gtatgcagag gctcggagac
                                                                           180
 ggatectagg cagtgccage cet
                                                                           203
       <210> 102
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<211> 300

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      <213> mouse
      <400> 102
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agccaacccc aactcagcca tctttggggg agccaggccc agagaggaag tggttcagaa
                                                                       120
ggagcaagaa tgagcttagg ttgggaggga atggggcgtg ggggagctgg agcaagacca
                                                                       180
eggeetggtg geageeggte geectacagg ecceatteee geetggeact gteeteetta
                                                                       240
cageggaaac acagagettg tgagtgcatg tcagetgtta acaagtggtt tctagtacat
                                                                       300
      <210> 103
<211> 370
      <212> DNA
      <213> mouse
      <220>
      <400> 103
cagcaactgt ttcaggagct gcacggtgta cgcctgctga ctgatgcgct ggaactaaca
                                                                        60
ctgggcgtgg cccccaaaga aaaccctccg gtgatgcttc cagcccaaga gacggagagg
                                                                       120
gccatggaga tcctcaaagt gctctttaat atcacctttg actctgtcaa gagggaagtt
                                                                       180
gatgaggaag atgctgccct ttaccggtac ctggggactc ttctgcggca ctgcgtgatg
                                                                       240
gttgaagctg ctggggaccg cacagaggag ttccacggcc acacggtgaa tctcctgggg
                                                                       300
aacttgcccc tcaagtgttt ggatgtgctt ctggccctgg agctccacga aggatcctta
                                                                       360
gagtcaatgg
                                                                       370
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      <211> 423
      <212> DNA
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tectacettg cetgtettet eteteetggg aagatgttee tggtgggget gaegggagge
                                                                       120
atogoctcag gcaagagete cgtcatccag gtattccaac agetgggetg tgctgtaate
                                                                       180
gacgtggacg tcattgcgcg gcacgttgtc cagccagggt atcctgccca ccggcgtata
                                                                       240
gtagaggeet tiggeactga agtetigetg gagaatggeg acategaceg caaggteete
                                                                       300
ggagacctga tcttcaacca gcctgaccgt cggcagctgc tcaactccat tacccaccct
                                                                       360
gagateegea aggaaatgat gaaggagaee tteaagtaet teteegaggt aeegataegt
                                                                       420
gat
                                                                       423
      <210> 105
      <211> 117
      <212> DNA
     <213> mouse
     <400> 105
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                                                                        60
geocgegteg gtgactgggg tetcacacag gttcagcact tggagcatag tgaggtg
                                                                       117
     <210> 106
      <211> 133
      <212> DNA
      <213> mouse
     <400> 106
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ttttttttt aaaataccac catttccaat cccaaaagaa catggcactt gtttgtttct
                                                                      60
teceettete atteatteea gaettteaag tgttttette aatactgagg ettteteetg
                                                                      120
cagetetggt etg
      <210>, 107
      <211> 217
      <212> DNA
      <213> mouse
      <220>
      <221> unsure
      <222> (1)...(1)
      <221> unsure
      <222> (11)...(11)
      <221> unsure
      <222> (18)...(23)
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      <222> (34) ... (34)
      <221> unsure
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      <221> unsure
      <222> (40)...(42)
      <221> unsure
      <222> (50)...(52)
      <221> unsure
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      <221> unsure
      <222> (152)...(152)
     <221> unsure
     <222> (155)...(155)
     <221> unsure
     <222> (165)...(165)
     <400> 107
ntttttttt ngcgcacnnn nnngnnnncg cccnggnngn nnagcctacn nncannnngt
                                                                      60
tttettetee aggetgaaga cetgaacgte aagttggaag gggageette catgeggaaa
                                                                     120
ccaaagcagc ggccgcgcc ggagcccctc ancancccca ccaangeggg cactttcatc
                                                                     180
geocetectg tetactecaa cateaccect taccaga
                                                                     217
     <210> 108
     <211> 346
     <212> DNA
     <213> mouse
     <220>
     <400> 108
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gggcatagaa ggcatctcga aaagaatact tatttgaatt gaaggaagat gaagaggcct
                                                                        60
 gcaggaaggc tcagaagaca ggagtgtttt acctctttca tgacctggat cctttgctcc
                                                                      120
 aggogtcagg acatogatac ctggtgcccc ggcttagccg agcagagttg gaagggctgc
                                                                       180
 tgggtaagtt cggacaggat tcgcaaagaa ttgaagattc ggtgctggtt gggtgctccg
                                                                       240
 agcagcagga agcatggttt gctttggatc taggtctgaa gagtgcctcc tccagccgtg
                                                                       300
 gacaagtate getgeteeag cagettgaet getgtaaaga ggatet
                                                                     . 346
       <210> 109
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       <212> DNA
       <213> mouse
      <400> 109
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                                                                        60
 ttacaageta gagggtggcc ggcgagtaac cccgcccaag gggaggattg tccttgatgg
                                                                       120
 ctgcaccatc acctgcccct gcctggagta tgaaaaccgg ccgctcctca ttaaactgaa
                                                                       180
 gacccgaact tocactgagt acttoctgga agcctgttot cgagaggaga gagactcctg
                                                                       240
                                                                       242
       <210> 110
       <211> 310
      <212> DNA
       <213> mouse
     <220>
       <221> misc_feature
       <222> (1)...(310)
       <223> n = A,T,C or G
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eggeteece geggeeegee eteetgeegg cetegeegeg gteteeettg eteeetgaga
tegetgageg etgageageg geeegggaga ggaggeettg ggegaegggg egeggagagg
                                                                      180
gaggggggc gggcantggg ggcgccgcgg atctctatat ggcgacgggt ctgtcgggtc
                                                                      240
tggetgteeg getgtegege teggeeggne ggeeggttee tatggggtet tetgeaaagg
                                                                      300
ggttgacccg
                                                                      310
       <210> 111
       <211> 228
       <212> DNA
       <213> mouse
       <400> 111
                                                                        .48
 ttcttttta acatttggtg gtttttttct ttactctttt tttcttttcc ttcttttct
                                                                        60
 gccctcaacc ccccaactcc tttggtatga agtactttta acatttatat ttcattgtta
                                                                       120
 cactttaaat tttgtaagga aaactctgat atttcattcc tcctgaacca ctaatgttag
                                                                       180
 aatttatttc taagaatcag tcaacatgta tactcttaat agtgaatt
                                                                       228
      <210> 112
       <211> 292
       <212> DNA
       <213> mouse
       <400> 112
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                                                                        60
 ctggtggcat ggactatggt atggttggtg gcaaggaggc tgggaccgag tctcgcttca
                                                                       120
 aacagtggac ctcaatgatg gaagggctgc.catctgtggc cacacaagaa gccaccatgc
                                                                       180
```

				aggttcacca tcctgctggt		240 292
<210><211><211>	255 DNA					
<2132	mouse	•				
<220>	•					
`< <b>4</b> 00>						
				tgaaaacact tatagtgttg		60 120
				ggcaggggtg		180
				tcttctactt		240
acgagagtca						255
<210	> 114		•			
<211:						
	> DNÁ					
<213	> mouse				•	
<400				•		
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				gtaagaaacc		120
		tttttttt	aaagatgaca	aatgtacaga	tgttagtaca	180 197
gatgttaatg	tacagat					197
	> 115				•	
	> 205				•	
	> DNA > mouse					
<213	· mouse					
	> 115					
				aaaaaaacaa		60
				gtgttccagg		120
-	gttatagaca		tttcactcaa	tatattatga	caacacacac	180 205
LLAGGALLEL	gicalayaca	aaaaa				203
	> 116					,
	> 202					
	> DNA > mouse				·	
<b>&lt;213</b> .	> mouse				•	-
<220	· ·					•
	•					
	> 116 '			•		
				tttctcattc		60
				cgcacacaca		120 180
	gtcagtgcct		acttagtttt	ccattcctag	ayayacctaa	202
CORCUCCIO	accad racet	ua				
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	> 240					
	> DNA		,			

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cgcttctgct gtgtgaagga gcgcaagccc tggagtgcta cagctgcgtg cagaaggcgg
                                                                    120
acgatggatg cgctccgcac aggatgaaga cagtcaaatg tggtcccggg gtggacgtct
                                                                    180
gtaccgagge cgtgggageg gtagagacca tccacgggca attctctgtg geggtgeggg
                                                                    240
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      <211> 527
      <212> DNA
      <213> Human
      <400> 118
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gttccaatat cagtctatct tttattcaac gcaatgacag cactgaccga agaggcagcc
                                                                    120
gtgactgtaa cacctccaat cacagcccag caaggtaact ggacagttaa caaaacagaa
                                                                    180
getcacaaca tagaaggace catageettg aagttetcac acetttgeet ggaagateat
                                                                    240
aacagttact gcatcaacgg tgcttgtgca ttccaccatg agctagagaa agccatctgc
                                                                    300
aggigittia ciggitatac iggagaaagg igigagcact igactitaac itcataigci
                                                                    360
gtggattett atgaaaaata cattgcaatt gggattggtg ttggattact attaagtggt
                                                                    420
tttcttgtta ttttttactg ctatataaga aagaggtgtc taaaattgaa atcgccttac
                                                                    480
aatgtctgtt ctggagaaag acgaccactg tgaggccttt gtgaaga
                                                                    527
      <210> 119
      <211> 655
      <212> DNA
      <213> Rat
      <400> 119
atggcgcgcc ccgcgccctg gtggtggctg cggccgctgg cggcgctcgc cctggcgctg
gegetggtee gggtgeeete ageeegggee gggeagatge egegeeeege agagegeggg
                                                                    180
ccccagtac ggctcttcac cgaggaggag ctggcccgct acagcggcga ggaggaggat
caacccatct acttggcagt gaagggagtg gtgttcgatg tcacctctgg gaaggagttt
                                                                    240
tatggacgtg gagcccccta caacgccttg gccgggaagg actcgagcag aggtgtggcc
                                                                    300
aagatgtege tggateetge agaceteaet catgacattt etggteteae tgecaaggag
                                                                    360
ctggaagece tegatgacat etteageaag gtgtacaaag ccaaatacce cattgttgge
                                                                    420
tacacggccc gcaggatect caacgaggat ggcageccca acetggactt caageetgaa
                                                                    480
gaccagecee attitgacat aaaggacgag ttetaatgte tagetgagaa getggtteta
                                                                    540
gggagaggtg agggacagg agttaaatgt cccacggaac aagcagggga agcctctgag
                                                                    600
                                                                    655
<210> 120
      <211> 176
      <212> PRT
      <213> Rat
      <400> 120
Met Val Pro Cys Phe Leu Leu Ser Leu Leu Leu Val Arg Pro Ala
Pro Val Val Ala Tyr Ser Val Ser Leu Pro Ala Ser Phe Leu Glu Glu
           20
                              25
Val Ala Gly Ser Gly Glu Ala Glu Gly Ser Ser Ala Ser Ser Pro Ser
       35
                                            · 45
                          40
Leu Leu Pro Pro Arg Thr Pro Ala Phe Ser Pro Thr Pro Gly Arg Thr
Gln Pro Thr Ala Pro Val Gly Pro Val Pro Pro Thr Asn Leu Leu Asp
                   70
```

```
Gly Ile Val Asp Phe Phe Arg Gln Tyr Val Met Leu Ile Ala Val Val
                85
                                     90
Gly Ser Leu Thr Phe Leu Ile Met Phe Ile Val Cys Ala Ala Leu Ile
100 105 110
Thr Arg Gln Lys His Lys Ala Thr Ala Tyr Tyr Pro Ser Ser Phe Pro
115 120 125
Glu Lys Lys Tyr Val Asp Gln Arg Asp Arg Ala Gly Gly Pro His Ala
130 135 140
Phe Ser Glu Val Pro Asp Arg Ala Pro Asp Ser Arg Gln Glu Glu Gly 145 155 160
                             155
                                                            160
Leu Asp Phe Phe Gln Gln Leu Gln Ala Asp Ile Leu Ala Cys Tyr Ser
165 170 175
        165
      <210> 121
      <211> 116
      <212> PRT
      <213> Rat
      <400> 121
Met Glu Leu Leu Tyr Trp Cys Leu Leu Cys Leu Leu Leu Pro Leu Thr
                                    10
Ser Arg Thr Gln Lys Leu Pro Thr Arg Asp Glu Glu Leu Phe Gln Met 20 25 30
Gln Ile Arg Asp Lys Ala Leu Phe His Asp Ser Ser Vai Ile Pro Asp
       35
                           40
                                                 45
Gly Ala Glu Ile Ser Ser Tyr Leu Phe Arg Asp Thr Pro Arg Arg Tyr 50 60
Phe Phe Met Val Glu Glu Asp Asn Thr Pro Leu Ser Val Thr Val Thr 65 70 75 80
Pro Cys Asp Ala Pro Leu Glu Trp Lys Leu Ser Leu Gln Glu Leu Pro
85 90 95
Glu Glu Ser Ser Ala Asp Gly Ser Gly Asp Pro Glu Pro Leu Asp Gln
           100
                                 105
Gln Lys Gln Gln
        115
      <210> 122
      <211> 64
      <212> PRT
      <213> Human
      <400> 122
Met Asn Leu Leu Ile Gly Ser Ile Ile Leu Ser Ser Phe Leu Val Leu
              5
                                     10
                                                         15
Ser Asp Gly Asp Thr Thr Ala Ser Pro Ser Ser Met Ser Ser Ser Ser
                              25
Val Leu Asn His Ile Ser Ser Ser Ser Ser Ser Val Trp His Leu Phe 35 40 45
Asp Ile Cys Asp Ser Ser Lys Trp Asn Ala Tyr Cys Gln Val Trp Gly
                        55
                                              60
      <210> 123
      <211> 68
      <212> PRT
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<213> Human <400> 123

<210> 124 <211> 110 <212> PRT

<213> mouse

<210> 125 <211> 330 <212> PRT <213> mouse

 <400> 125

 Met Gly Ser Pro Arg Leu Ala Val Ser Ala Ala Leu Leu Leu Ser Leu Pro Leu Leu 1
 5
 10
 15
 15

 Leu Ile Gly Leu Ala Val Ser Ala Arg Val Ala Cys Pro 20
 25
 30
 25
 25
 30

 Ser Trp Thr Ser His Cys Leu Leu Ala Tyr Arg Val Asp Lys Arg Phe 35
 40
 40
 45
 45

 Ala Gly Leu Gln Trp Gly Trp Phe Pro Leu Leu Val Arg Lys Ser Lys 50
 55
 60
 60
 55
 80

 Ser Pro Pro Pro Lys Phe Glu Asp Tyr Trp Arg His Arg Thr Pro Ala Ser 75
 80
 80
 85
 80

 Phe Gln Arg Lys Leu Leu Gly Ser Pro Ser Leu Ser Glu Glu Ser His 85
 90
 95

 Arg Ile Ser Ile Pro Ser Ser Ala Ile Ser His Arg Gly Gln Arg Thr 100
 105
 110

 Lys Arg Ala Gln Pro Ser Ala Ala Glu Gly Arg Glu His Leu Pro Glu 115
 120
 125

 Ala Gly Ser Gln Lys Cys Gly Gly Pro Glu Phe Ser Phe Asp Leu Leu 130
 140

 Pro Glu Val Gln Ala Val Arg Val Thr Ile Pro Ala Gly Pro Lys Ala

```
150
                                               155
Ser Val Arg Leu Cys Tyr Gln Trp Ala Leu Glu Cys Glu Asp Leu Ser
165 170 175
Ser Pro Phe Asp Thr Gln Lys Ile Val Ser Gly Gly His Thr Val Asp
180 185 190
Leu Pro Tyr Glu Phe Leu Leu Pro Cys Met Cys Ile Glu Ala Ser Tyr
195 200 205

Leu Gln Glu Asp Thr Val Arg Arg Lys Lys Cys Pro Phe Gln Ser Trp
210 215 220
Pro Glu Ala Tyr Gly Ser Asp Phe Trp Gln Ser Ile Arg Phe Thr Asp 225 230 235 240
Tyr Ser Gln His Asn Gln Met Val Met Ala Leu Thr Leu Arg Cys Pro
245 250 255
Leu Lys Leu Glu Ala Ser Leu Cys Trp Arg Gln Asp Pro Leu Thr Pro 260 265 270
Cys Glu Thr Leu Pro Asn Ala Thr Ala Gln Glu Ser Glu Gly Trp Tyr 275 280 285
Ile Leu Glu Asn Val Asp Leu His Pro Gln Leu Cys Phe Lys Phe Ser 290 295 300
Phe Glu Asn Ser Ser His Val Glu Cys Pro His Gln Ser Gly Ser Leu 305 310 315 320
Pro Ser Trp Thr Val Ser Met Asp Thr Gln
        325·
                                          330
       <210> 126
       <211> 37
       <212> PRT
       <213> Rat
       <400> 126
Met Leu Trp Val Leu Leu Ser Leu Thr Pro Leu Leu Ser Pro Leu Ile
1 5 10 15
Phe Phe Pro Val Lys Thr Val Ala Leu Glu Glu Ile Ser Thr Ile Cys
     20
Arg Ala Asp Val Leu
      35
       <210> 127
       <211> 42
       <212> PRT
       <213> mouse
       <400> 127
Met Gly Ser Pro Ile Ser Gly Val Cys Pro Val Leu Pro Gly Gly Leu
                                       10
Phe Val Ala Leu Gly Trp Ile Phe Leu Leu Phe His Arg Asp Ala Phe 20 25 30
Ser Leu His Thr Met Ser Ala Gly Phe Pro
        35
                                40
       <210> 128
       <211> 253
       <212> PRT
       <213> mouse
      <400> 128
```

Met Met Tyr Trp Ile Val Phe Ala Ile Phe Met Ala Ala Glu Thr Phe

```
10
Thr Asp Ile Phe Ile Ser Trp Ser Gly Pro Arg Ile Gly Arg Pro Trp 20 25 30
Gly Trp Glu Gly Pro His His His His Leu Ala Ser Gly Ser His
       35 .
                             40
                                                    45
Lys Pro Leu Pro Leu Eu Thr His Arg Phe Pro Phe Tyr Tyr Glu Phe 50 55 60
Lys Met Ala Phe Val Leu Trò Leu Leu Ser Pro Tyr Thr Lys Gly Ala 65 70 75 80
Ser Leu Leu Tyr Arg Lys Phe Val His Pro Ser Leu Ser Arg His Glu
85 90 95
Lys Glu Ile Asp Ala Cys Ile Val Gln Ala Lys Glu Arg Ser Tyr Glu
100 105 110
Thr Met Leu Ser Phe Gly Lys Arg Ser Leu Asn Ile Ala Ala Ser Ala
115 120 125
Ala Val Gln Ala Ala Thr Lys Ser Gln Gly Ala Leu Ala Gly Arg Leu
130 135 140
Arg Ser Phe Ser Met Gln Asp Leu Arg Ser Ile Pro Asp Thr Pro Val
145 150 155 160
Pro Thr Tyr Gln Asp Pro Leu Tyr Leu Glu Asp Gln Val Pro Arg Arg
165 170 175
Arg Pro Pro Ile Gly Tyr Arg Pro Gly Gly Leu Gln Gly Ser Asp Thr
180 185 190
Glu Asp Glu Cys Trp Ser Asp Asn Glu Ile Val Pro Gln Pro Pro Val
195 200 205
Arg Pro Arg Glu Lys Pro Leu Gly Arg Ser Gln Ser Leu Arg Val Val 210 215 220
Lys Arg Lys Pro Leu Thr Arg Glu Gly Thr Ser Arg Ser Leu Lys Val
225 230 235 240
Arg Thr Arg Lys Lys Ala Met Pro Ser Asp Met Asp Ser 245 250
      <210> 129
      <211> 40
      <212> PRT
      <213> mouse
      <400> 129
Met Lys Ala Met Ala Leu Ser Leu Gly Ala Ser Pro Val Leu Ala Phe 1 5 10 15
             5
Leu Leu Ser Gly Tyr Ser Asp Gly Tyr Gln Val Cys Ser Arg Phe Gly 20 25 30
Ser Lys Val Pro Gln Phe Leu Asn
        35
      <210> 130
<211> 87
       <212> PRT
       <213> mouse
       <400> 130
Met Ile Ala Val Thr Phe Ala Ile Val Leu Gly Val Ile Ile Tyr Arg
1 5 10 15
                  5
                                       10
Ile Ser Thr Ala Ala Ala Leu Ala Met Asn Ser Ser Pro Ser Val Arg
      20
                                  25
                                                       30
Ser Asn Ile Arg Val Thr Val Thr Ala Thr Ala Val Ile Ile Asn Leu
```

40,

```
Val Val Ile Ile Leu Leu Asp Glu Val Tyr Gly Cys Ile Ala Arg Trp 50 55 60
Leu Thr Lys Ile Gly Glu Cys His Val Gln Asp Ser Ile Gly Ser Met
                  70
Gly Leu Gly Gln Gly Gln Pro
               85
     <210> 131
     <211> 70
     <212> PRT
     <213> mouse
     <400> 131
Met Phe Gly Leu Val His Val Cys Thr Cys Val Cys Val Cys Val Cys
                                 10
Val Cys Val Cys Val Cys Ile Cys Ser Cys Gly Tyr Val His Val Pro
20 25 30
Cys Gly Cys Val Cys Leu Trp Gly Pro Glu Val Arg Tyr Leu Pro Leu
35 40 45
Ser Leu His Pro Gly Gly Phe Cys Phe Val Leu Phe Cys Phe Gly Pro
  50
Gly Leu Ser Leu Ile Ser
     <210> 132
     <211> 63
     <212> PRT
     <213> mouse
   ' <400> 132
Met Trp Leu Leu Val Ala Leu Thr Leu Ser Val Tyr Ser Leu Val Ala
                                10
Phe Val Thr Gly Met Leu Cys Asp Thr Val Val Ile Lys Met Leu Met
        20
                            25
                                               30
Ser Leu His Lys Ser Ser Lys Leu Asn Pro Arg Ala Lys Cys Gly Gly
   35
                        40
                                           45
Val Pro Leu Ile Pro Ala Leu Trp Gly Gln Val Gln Val Val Leu
   50
                      55
                                         60
     <210> 133
     <211> 39
     <212> PRT
     <213> mouse
     <400> 133
Ile Ser Val Leu Asp Ser Gln Leu Ser Thr Arg Cys Leu Trp Trp Phe 20 25 30
Ser Lys Asp Leu Glu Val Thr
      35
     <210> 134
     <211> 90
     <212> PRT
     <213> Rat
```

```
<400> 134
Met Pro Thr Met Trp Pro Leu Leu His Val Leu Trp Leu Ala Leu Val
                                        10
Cys Gly Ser Val His Thr Thr Leu Ser Lys Ser Asp Ala Lys Lys Ala 20 25 30
Ala Ser Lys Thr Leu Leu Glu Lys Thr Gln Phe Ser Asp Lys Pro Val
Gln Asp Arg Gly Leu Val Val Thr Asp Ile Lys Ala Glu Asp Val Val 50 60
Leu Glu His Arg Ser Tyr Cys Ser Ala Arg Ala Arg Glu Arg Asn Phe 65 70 75 80
Ala Gly Glu Val Leu Gly Ile Cys His Ser
                  85
       <210> 135
       <211> 193
       <212> PRT
       <213> Rat
       <400> 135
Met Thr Ser Gly Pro Gly Gly Pro Ala Ala Ala Thr Gly Gly Gly Lys 1 \hspace{1.5cm} 5 \hspace{1.5cm} 10 \hspace{1.5cm} 15
Asp Thr His Gln Trp Tyr Val Cys Asn Arg Glu Lys Leu Cys Glu Ser
20 25 30
Leu Gln Ser Val Phe Val Gln Ser Tyr Leu Asp Gln Gly Thr Gln Ile 35 40 45
Phe Leu Asn Asn Ser Ile Glu Lys Ser Gly Trp Leu Phe Ile Gln Leu 50 55 60
Tyr His Ser Phe Val Ser Ser Val Phe Thr Leu Phe Met Ser Arg Thr 65 70 75 80
Ser Ile Asn Gly Leu Leu Gly Arg Gly Ser Met Phe Val Phe Ser Pro
85 90 95
Asp Gln Phe Gln Arg Leu Leu Lys Ile Asn Pro Asp Trp Lys Thr His 100 . 105 110
Arg Leu Leu Asp Leu Gly Ala Gly Asp Gly Glu Val Thr Lys Ile Met 115 120 125
Ser Pro His Phe Glu Glu Ile Tyr Ala Thr Glu Leu Ser Glu Thr Met
130 135 140
Ile Trp Gln Leu Gln Lys Lys Lys Tyr Arg Val Leu Gly Ile Asn Glu
145 150 155 160
Trp Gln Asn Thr Gly Phe Gln Tyr Asp Val IIe Ser Cys Leu Asn Leu
165 170 175
Leu Asp Arg Cys Asp Gln Pro Leu Thr Leu Leu Lys Asp Ile Arg Met
             180
                                     185
       <210> 136
       <211> 106
       <212> PRT
       <213> Rat
```

Met Ala Ala Pro Met Asp Arg Thr His Gly Gly Arg Ala Ala Arg Ala 1 5 10 15 Leu Arg Arg Ala Leu Ala Leu Ala Ser Leu Ala Gly Leu Leu Leu Ser

20

```
Gly Leu Ala Gly Ala Leu Pro Thr Leu Gly Pro Gly Trp Arg Arg Gln
                               40
Asn Pro Glu Pro Pro Ala Ser Arg Thr Arg Ser Leu Leu Leu Asp Ala
   50
Ala Ser Gly Gln Leu Arg Leu Glu Tyr Gly Phe His Pro Asp Ala Val
65 70 75 80
Ala Trp Ala Asn Leu Thr Asn Ala Ile Arg Glu Thr Gly Trp Ala Tyr 85 \, 90 \, 95
                85
Leu Asp Leu Gly Thr Asn Gly Ser Tyr Lys
            100
       <210> 137
       <211> 286
       <212> PRT
       <213> Rat
       <400> 137
Met Ala Ala Met Pro Leu Gly Leu Ser Leu Leu Leu Leu Val Leu 1 \cdot 5 \cdot 10 \cdot 15
Val Gly Gln Gly Cys Cys Gly Arg Val Glu Gly Pro Arg Asp Ser Leu
20 25 30
Arg Glu Glu Leu Val Ile Thr Pro Leu Pro Ser Gly Asp Val Ala Ala 35 40 45
Thr Phe Gin Phe Arg Thr Arg Trp Asp Ser Asp Leu Gln Arg Glu Gly 50 55 60
Val Ser His Tyr Arg Leu Phe Pro Lys Ala Leu Gly Gln Leu Ile Ser
65 70 75 80
Lys Tyr Ser Leu Arg Glu Leu His Leu Ser Phe Thr Gln Gly Phe Trp
85 90 95
Arg Thr Arg Tyr Trp Gly Pro Pro Phe Leu Gln Ala Pro Ser Gly Ala 100 105 110
Glu Leu Trp Val Trp Phe Gln Asp Thr Val Thr Asp Val Asp Lys Ser
115 120 125
Trp Lys Glu Leu Ser Asn Val Leu Ser Gly Ile Phe Cys Ala Ser Leu
130 135 140
Asn Phe Ile Asp Ser Thr Asn Thr Val Thr Pro Thr Ala Ser Phe Lys
145 150 155 160
Pro Leu Gly Leu Ala Asn Asp Thr Asp His Tyr Phe Leu Arg Tyr Ala
165 170 175
Val Leu Pro Arg Glu Val Val Cys Thr Glu Asn Leu Thr Pro Trp Lys
180 185 190
Lys Leu Pro Cys Ser Ser Lys Ala Gly Leu Ser Val Leu Leu Lys
195 200 205
Ala Asp Arg Leu Phe His Thr Ser Tyr His Ser Gln Ala Val His Ile
210 215 220
Arg Pro Ile Cys Arg Asn Ala His Cys Thr Ser Ile Ser Trp Glu Leu 225 230 235 240

Arg Gln Thr Leu Ser Val Val Phe Asp Ala Phe Ile Thr Gly Gln Gly 245 250 255
Lys Lys Glu Ala Cys Pro Leu Ala Ser Gln Ser Leu Val Tyr Val Asp
           260 265 270
Ile Thr Gly Tyr Ser Gln Asp Asn Glu Thr Leu Glu Val Ser
                         . 280
```

<210> 138 <211> 198 <212> PRT

<213> Rat

<400> 138 Met Thr Val Phe Arg Lys Val Thr Thr Met Ile Ser Trp Met Leu Leu 1 5 10 15 Ala Cys Ala Leu Pro Cys Ala Ala Asp Pro Met Leu Gly Ala Phe Ala 20 25 30 Arg Arg Asp Phe Gln Lys Gly Gly Pro Gln Leu Val Cys Ser Leu Pro 35 40 45 Gly Pro Gln Gly Pro Pro Gly Pro Pro Gly Ala Pro Gly Ser Ser Gly 50 55 60 Met Val Gly Arg Met Gly Phe Pro Gly Lys Asp Gly Gln Asp Gly Gln 65 70 75 80 Asp Gly Asp Arg Gly Asp Ser Gly Glu Glu Gly Pro Pro Gly Arg Thr 85 90 95 Gly Asn Arg Gly Lys Gln Gly Pro Lys Gly Lys Ala Gly Ala Ile Gly 100 105 110 Arg Ala Gly Pro Arg Gly Pro Lys Gly Val Ser Gly Thr Pro Gly Lys 115 120 125 His Gly Ile Pro Gly Lys Lys Gly Pro Lys Gly Lys Lys Gly Glu Pro 130 135 140 Gly Leu Pro Gly Pro Cys Ser Cys Gly Ser Ser Arg Ala Lys Ser Ala 145 150 155 160 Phe Ser Val Ala Val Thr Lys Ser Tyr Pro Arg Glu Arg Leu Pro Ile 165 170 Lys Phe Asp Lys Ile Leu Met Asn Glu Gly Gly His Tyr Asn Ala Ser 180 185 190 Ser Gly Lys Phe Val Cys 195

<210> 139 <211> 233 <212> PRT <213> Rat

| Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Color | Colo

170

```
Lys Glu Lys Pro Ser Tyr Asp Thr Glu Ala Asp Pro Ser Glu Gly Leu
180 185 190
Met Asn Val Leu Lys Lys Ile Tyr Glu Asp Gly Asp Asp Met Lys
195 200 205
Arg Thr Ile Asn Lys Ala Trp Val Glu Ser Arg Glu Lys Gln Ala Arg 210 225 220
Glu Asp Thr Glu Phe Leu Gln Pro Gly
                      230
      <210> 140
      <211> 38
      <212> PRT
      <213> Human
      <400> 140
Met Gly Leu Ala Leu Cys Leu Ala Ser Ala Gly Ile Ser Gly Ser Arg
                  5
                                     10
Ser Ala Phe Leu Gly Val Pro Arg Pro Arg Pro Thr Leu Ile Lys Leu 20 25 30
Ile Asp Thr Val Asp Leu
       35
      <210> 141
      <211> 322
      <212> PRT
      <213> mouse
      <400> 141
Met Asp Ala Arg Trp Trp Ala Val Val Leu Ala Thr Leu Pro Ser
                                   10
Leu Gly Ala Gly Glu Ser Pro Glu Ala Pro Pro Gln Ser Trp Thr 20 25 30
Gln Leu Trp Leu Phe Arg Phe Leu Leu Asn Val Ala Gly Tyr Ala Ser
35 40 45
Phe Met Val Pro Gly Tyr Leu Leu Val Gln Tyr Leu Arg Arg Lys Asn
50 55 60
Tyr Leu Glu Thr Gly Arg Gly Leu Cys Phe Pro Leu Val Lys Ala Cys 65 70 75 80
Val Phe Gly Asn Glu Pro Lys Ala Pro Asp Glu Val Leu Leu Ala Pro
                85
                                    90
Arg Thr Glu Thr Ala Glu Ser Thr Pro Ser Trp Gln Val Leu Lys Leu 100 105 110
Val Phe Cys Ala Ser Gly Leu Gln Val Ser Tyr Leu Thr Trp Gly Ile
115 120 125
Leu Gln Glu Arg Val Met Thr Gly Ser Tyr Gly Ala Thr Ala Thr Ser 130 135 140 .
Pro Gly Glu His Phe Thr Asp Ser Gln Phe Leu Val Leu Met Asn Arg
145 150 155 160
Val Leu Ala Leu Val Val Ala Gly Leu Tyr Cys Val Leu Arg Lys Gln
165 170 175
Pro Arg His Gly Ala Pro Met Tyr Arg Tyr Ser Phe Ala Ser Leu Ser
180 190
Asn Val Leu Ser Ser Trp Cys Gln Tyr Glu Ala Leu Lys Phe Val Ser
195 200 205
                            200
Phe Pro Thr Gln Val Leu Ala Lys Ala Ser Lys Val Ile Pro Val Met
```

215

220

 Met
 Met
 Gly
 Leu
 Val
 Ser
 Arg
 Ser
 Tyr
 Glu
 His
 Txp
 Glu
 Tyr
 Q40

 Leu
 Thr
 Ala
 Gly
 Leu
 Ile
 Ser
 Ile
 Gly
 Val
 Ser
 Met
 Phe
 Leu
 Leu
 Leu
 Ser
 Ser
 Fro
 Val
 Ser
 Met
 Phe
 Phe
 Leu
 Leu
 Leu
 Leu
 Asa
 Ser
 Ser
 Pro
 Ala
 Thr
 Thr
 Thr
 Leu
 Ser
 Gly
 Leu
 Asa
 Try
 Leu
 Asa
 Phe
 Try
 Try
 Asa
 Phe
 Asa
 Try
 <210> 142 <211> 312 <212> PRT <213> mouse

<400> 142 Met Leu Cys Leu Cys Leu Tyr Val Pro Ile Ala Gly Ala Ala Gln Thr 1 5 10 15 Glu Phe Gln Tyr Phe Glu Ser Lys Gly Leu Pro Ala Glu Leu Lys Ser 20 25 30 Ile Phe Lys Leu Ser Val Phe Ile Pro Ser Gln Glu Phe Ser Thr Tyr 35 40 45 Arg Gln Trp Lys Gln Lys Ile Val Gln Ala Gly Asp Lys Asp Leu Asp 50 60 Gly Gln Leu Asp Phe Glu Glu Phe Val His Tyr Leu Gln Asp His Glu 65 70 75 80 Lys Lys Leu Arg Leu Val Phe Lys Ser Leu Asp Lys Lys Asn Asp Gly 85 90 95 Arg Ile Asp Ala Gln Glu Ile Met Gln Ser Leu Arg Asp Leu Gly Val Lys Ile Ser Glu Gln Gln Ala Glu Lys Ile Leu Lys Ser Met Asp Lys 115 120 125 Asn Gly Thr Met Thr Ile Asp Trp Asn Glu Trp Arg Asp Tyr His Leu 130 135 140 Leu His Pro Val Glu Asn Ile Pro Glu Ile Ile Leu Tyr Trp Lys His 145 150 155 160 Ser Thr Ile Phe Asp Val Gly Glu Asn Leu Thr Val Pro Asp Glu Phe 165 170 175 Thr Val Glu Glu Arg Gln Thr Gly Met Trp Trp Arg His Leu Val Ala 180 185 190 Gly Gly Gly Ala Gly Ala Val. Ser Arg Thr Cys Thr Ala Pro Leu Asp 195 200 205 Arg Leu Lys Val Leu Met Gln Val His Ala Ser Arg Ser Asn Asn Met 210 215 220 Cys Ile Val Gly Gly Phe Thr Gln Met Ile Arg Glu Gly Gly Ala Lys 225 230 235 240 Ser Leu Trp Arg Gly Asn Gly Ile Asn Val Leu Lys Ile Ala Pro Glu 245 250 255 Ser Ala Ile Lys Phe Met Ala Tyr Glu Gln Met Lys Arg Leu Val Gly 260 265 270 Ser Asp Gln Glu Thr Leu Arg Ile His Glu Arg Leu Val Ala Gly Ser 280 . . 285

```
Leu Ala Gly Ala Ile Ala Gln Ser Ser Ile Tyr Pro Met Glu Val Leu 290 295 300
Lys Thr Arg Met Ala Leu Arg Lys
305
                   310
      <210> 143
      <211> 163
      <212> PRT
      <213> Rat
      <400> 143
Met Pro Leu Val Thr Thr Leu Phe Tyr Ala Cys Phe Tyr His Tyr Thr
                                   10
                                                         15
Glu Ser Glu Gly Thr Phe Ser Ser Pro Val Asn Leu Lys Lys Thr Phe 20 25 30
Lys Ile Pro Asp Arg Gln Tyr Val Leu Thr Ala Leu Ala Ala Arg Ala 35 40 45
Lys Leu Arg Ala Trp Asn Asp Val Asp Ala Leu Phe Thr Thr Lys Asn 50 60
Trp Leu Gly Tyr Thr Lys Lys Arg Ala Pro Ile Gly Phe His Arg Val 65 70 75 80
Val Glu Ile Leu His Lys Asn Ser Ala Pro Val Gln Ile Leu Gln Glu
85 90 95
Tyr Val Asn Leu Val Glu Asp Val Asp Thr Lys Leu Asn Leu Ala Thr 100 105 110
Lys Phe Lys Cys His Asp Val Val Ile Asp Thr Cys Arg Asp Leu Lys 115 ' 120 125
Asp Arg Gln Gln Leu Leu Ala Tyr Arg Ser Lys Val Asp Lys Gly Ser
130 135 140
Ala Glu Glu Lys Ile Asp Val Ile Leu Ser Ser Ser Gln Ile Arg
145
                   150
                                        155
Trp Lys Asn
      <210> 144
      <211> 330
      <212> PRT
      <213> Rat
      <400> 144
Ala Leu Trp Leu Leu Leu Ala Ala Ala Phe Leu Leu Ala Leu Leu Leu 20 25 30
Gln Leu Ala Pro Ala Arg Leu Leu Pro Ser Cys Ala Leu Phe Gln Asp 35 40 45
Leu Ile Arg Tyr Gly Lys Thr Lys Gln Ser Gly Ser Arg Arg Pro Ala 50 55 60
Val Cys Arg Ala Phe Asp Val Pro Lys Arg Tyr Phe Ser His Phe Tyr 65 70 75 80
Val Val Ser Val Leu Trp Asn Gly Ser Leu Leu Trp Phe Leu Ser Gln
85 90 95
```

 Ser
 Leu
 Phe
 Leu
 Gly
 Ala
 Pro
 Phe
 Pro
 Ser
 Trp
 Leu
 Trp
 Ala
 Leu
 Leu

 100
 105
 110
 110

 Arg
 Thr
 Leu
 Gly
 Val
 Thr
 Gln
 Phe
 Gln
 Ala
 Leu
 Gly
 Met
 Glu
 Ser
 Lys

 115
 120
 120
 125
 125

 Ala
 Ser
 Arg
 Ile
 Gln
 Ala
 Glu
 Leu
 Ala
 Leu
 Ser
 Thr
 Phe
 Leu
 Val

```
130
                                 135
                                                             140
Leu Val Phe Leu Trp Val His Ser Leu Arg Arg Leu Phe Glu Cys Phe
                         150
                                                   155
Tyr Val Ser Val Phe Ser Asn Thr Ala Ile His Val Val Gln Tyr Cys
                  165 170 175
Phe Gly Leu Val Tyr Tyr Val Leu Val Gly Leu Thr Val Leu Ser Gln
180 185 190

Val Pro Met Asn Asp Lys Asn Val Tyr Ala Leu Gly Lys Asn Leu Leu
195 200 205
Leu Gln Ala Arg Trp Phe His Ile Leu Gly Met Met Met Phe Phe Trp
210 215 220
Ser Ser Ala His Gln Tyr Lys Cys His Val Ile Leu Ser Asn Leu Arg
225 230 235 240
Arg Asn Lys Lys Gly Val Val Ile His Cys Gln His Arg Ile Pro Phe
245 250 255
Gly Asp Trp Phe Glu Tyr Val Ser Ser Ala Asn Tyr Leu Ala Glu Leu 260 265 270
Met Ile Tyr Ile Ser Met Ala Val Thr Phe Gly Leu His Asn Val Thr 275 280 285

Trp Trp Leu Val Val Thr Tyr Val Phe Phe Ser Gln Ala Leu Ser Ala 290 295 300
Phe Phe Asn His Arg Phe Tyr Lys Ser Thr Phe Val Ser Tyr Pro Lys 305 310 315 320
His Arg Lys Ala Phe Leu Pro Phe Leu Phe
         325
        <210> 145
```

<210> 145 <211> 301 <212> PRT <213> Rat

<400> 145 Met Leu Val Ala Phe Leu Gly Ala Ser Ala Val Thr Ala Ser Thr Gly 1 5 10 Leu Leu Trp Lys Lys Ala His Ala Glu Ser Pro Pro Ser Val Asn Ser . 20 . 25 30 Lys Lys Thr Asp Ala Gly Asp Lys Gly Lys Ser Lys Asp Thr Arg Glu 35 40 45 Val Ser Ser His Glu Gly Ser Ala Ala Asp Thr Ala Ala Glu Pro Tyr 50 55 60 Pro Glu Glu Lys Lys Lys Lys Arg Ser Gly Phe Arg Asp Arg Lys Val 65 70 75 80 Met Glu Tyr Glu Asn Arg Ile Arg Ala Tyr Ser Thr Pro Asp Lys Ile 85 90 95 Phe Arg Tyr Phe Ala Thr Leu Lys Val Ile Asn Glu Pro Gly Glu Thr 100 105 110 Glu Val Phe Met Thr Pro Gln Asp Phe Val Arg Ser Ile Thr Pro Asn 115 120 . 125 Glu Lys Gln Pro Glu His Leu Gly Leu Asp Gln Tyr Ile Ile Lys Arg 130 135 140 Phe Asp Gly Lys Lys Ile Ala Gln Glu Arg Glu Lys Phe Ala Asp Glu 145 150 155 160 Gly Ser Ile Phe Tyr Thr Leu Gly Glu Cys Gly Leu Ile Ser Phe Ser 165 170 175 Asp Tyr Ile Phe Leu Thr Thr Val Leu Ser Thr Pro Gln Arg Asn Phe 185 190 180 Glu Ile Ala Phe Lys Met Phe Asp Leu Asn Gly Asp Gly Glu Val Asp

```
200
       195
                                                 205
Met Glu Glu Phe Glu Gln Val Gln Ser Ile Ile Arg Ser Gln Thr Ser
   210
                     215
                                            220
Met Gly Met Arg His Arg Asp Arg Pro Thr Thr Gly Asn Thr Leu Lys
225 230 235 240
Ser Gly Leu Cys Ser Ala Leu Thr Thr Tyr Phe Phe Gly Ala Asp Leu 245 250 255
Lys Gly Lys Leu Thr Ile Lys Asn Phe Leu Glu Phe Gln Arg Lys Leu 260 265 270
Gln Arg Cys Leu Leu Gly Leu Pro Val Trp Glu Gly Ser Pro His Leu
275 280 285
Pro Thr Gly His Trp Leu Arg Glu Leu Trp Ser Leu Leu
                       295
                                           300
      <210> 146
      <211> 61
      <212> PRT
      <213> Rat
      <400> 146
Met Glu Asn Ile Tyr Tyr Thr Asn Leu Ile Thr Ile Leu Gly Asn Lys
His Ala Asn Gln Met Glu Leu Asn Leu Gln Ala Leu Ile Leu Ser Pro
                             25
      20
                                                  30
Trp Phe Ala Val Cys Ala Pro Pro Gly Phe Ala Arg Asp Gln Ala Val
      35
                           40
Arg Gly Leu Ala Leu Ala Gly Arg Arg Ile Thr Val Val
                       55
      <210> 147
      <211> 105
      <212> PRT
      <213> Rat
      <400> 147
Met Leu Arg Arg Gln Leu Val Trp Trp His Leu Leu Ala Leu Leu Phe
                                    10
Leu Pro Phe Cys Leu Cys Gln Asp Glu Tyr Met Glu Ser Pro Gln Ala
         20
                                25
Gly Gly Leu Pro Pro Asp Cys Ser Lys Cys Cys His Gly Asp Tyr Gly 35 40 45
Phe Arg Gly Tyr Gln Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Ile 50 55 60 .
Pro Gly Asn His Gly Asn Asn Gly Asn Asn Gly Ala Thr Gly His Glu 65 70 75 80
Gly Ala Lys Gly Glu Lys Gly Asp Lys Gly Asp Leu Gly Pro Arg Gly
85 90 - 95
Glu Arg Gly Gln His Gly Pro Lys Gly
       . 100
      <210> 148
      <211> 210
      <212> PRT
      <213> Rat
      <400> 148
```

Met Leu Gly Ala Thr Ser Leu Ser Trp Pro Trp Val Leu Trp Ala Val

```
Ala Gln Arg Asp Ser Val Asp Ala Ile Gly Met Phe Leu Gly Gly Leu
                                 25
Val Ala Thr Ile Phe Leu Asp Ile Ile Tyr Ile Ser Ile Phe Tyr Ser
35 40 45
Ser Val Ala Val Gly Asp Thr Gly Arg Phe Ser Ala Gly Met Ala Ile
50 55 60
Phe Ser Leu Leu Leu Gln Ala Leu Leu Leu Pro Arg Leu Pro His
65 70 75 80
Ala Pro Gly Ser Glu Gly Val Ser Ser Arg Ser Ala Arg Ile Ser Ser
85 90 95
Asp Leu Leu Arg Asn Ile Val Pro Thr Arg Gln Leu Thr Arg Gln Thr 100 105 110
His Leu Gln Thr Pro Leu Gln Ala Trp Arg Thr Arg Ala Lys Leu Pro
115 120 125
Pro Gly Gly Thr Glu Ala Val Pro Gly Arg Pro Gly Ala Gln Gln Asp
130 135 140
Ala Cys His Leu Leu Tyr Trp Thr Tyr Asn Gly Val Ser Ser Ile Pro
145 150 155 160
Cys His Arg Gly Gly Leu Ser His Val Pro Ser Glu Val Pro Ala Glu
165 170 175
Lys Ser Pro Val Leu Ile Leu His Ala Ala Pro Pro Phe Lys Thr Pro
                                   1.85
            180
                                                         190
Val Asn Pro Trp Ala Arg Thr Val Val Gly Phe Phe Pro Ser Ser Pro
       195
                               200
Ser Leu
   210
       <210> 149
       <211> 301
       <212> PRT
       <213> Rat
       <400> 149
Met Leu Val Ala Phe Leu Gly Ala Ser Ala Val Thr Ala Ser Thr Gly
                                        10
Leu Leu Trp Lys Lys Ala His Ala Glu Ser Pro Pro Ser Val Asn Ser
20 25 30
Lys Lys Thr Asp Ala Gly Asp Lys Gly Lys Ser Lys Asp Thr Arg Glu 35 40 45
Val Ser Ser His Glu Gly Ser Ala Ala Asp Thr Ala Ala Glu Pro Tyr
50 60
Pro Glu Glu Lys Lys Lys Lys Arg Ser Gly Phe Arg Asp Arg Lys Val
65 70 75 80
Met Glu Tyr Glu Asn Arg Ile Arg Ala Tyr Ser Thr Pro Asp Lys Ile
85 90 95
Phe Arg Tyr Phe Ala Thr Leu Lys Val Ile Asn Glu Pro Gly Glu Thr
100 105 110
Glu Val Phe Met Thr Pro Gln Asp Phe Val Arg Ser Ile Thr Pro Asn
115 120 125
Glu Lys Gln Pro Glu His Leu Gly Leu Asp Gln Tyr Ile Ile Lys Arg
130 135 140
Phe Asp Gly Lys Lys Ile Ala Gln Glu Arg Glu Lys Phe Ala Asp Glu
145 150 155 160
```

170

Gly Ser Ile Phe Tyr Thr Leu Gly Glu Cys Gly Leu Ile Ser Phe Ser

Asp Tyr Ile Phe Leu Thr Thr Val Leu Ser Thr Pro Gln Arg Asn Phe

165

```
180
                                185
                                                    190
Glu Ile Ala Phe Lys Met Phe Asp Leu Asn Gly Asp Gly Glu Val Asp
195 200 205
Met Glu Glu Phe Glu Gln Val Gln Ser Ile Ile Arg Ser Gln Thr Ser
 210 215
                                           220
Met Gly Met Arg His Arg Asp Arg Pro Thr Thr Gly Asn Thr Leu Lys
225 230 235 240
Ser Gly Leu Cys Ser Ala Leù Thr Thr Tyr Phe Phe Gly Ala Asp Leu 245 250 255
Lys Gly Lys Leu Thr Ile Lys Asn Phe Leu Glu Phe Gln Arg Lys Leu 260 265 270
Gln Arg Cys Leu Leu Gly Leu Pro Val Trp Glu Gly Ser Pro His Leu
275 280 285
Pro Thr Gly His Trp Leu Arg Glu Leu Trp Ser Leu Leu
                        295
      <210> 150
      <211> 80
      <212> PRT
      <213> Human
     <400> 150
Met Lys Leu Ser Gly Met Phe Leu Leu Leu Ser Leu Ala Leu Phe Cys
                                10
1 5
Phe Leu Thr Gly Val Phe Ser Gln Gly Gly Gln Val Asp Cys Gly Glu
20 25 30
Phe Gln Asp Thr Lys Val Tyr Cys Thr Arg Glu Ser Asn Pro His Cys 35 40 45
Gly Ser Asp Gly Gln Thr Tyr Gly Asn Lys Cys Ala Phe Cys Lys Ala
50 55 60
Ile Val Lys Ser Gly Gly Lys Ile Ser Leu Lys His Pro Gly Lys Cys
                    70
      <210> 151
      <211> 27
      <212> PRT
      <213> mouse
     <400> 151
Met Leu Lys Ala Ser Leu His Ile Leu Phe Leu Gly Ile Leu Asn Val
              5
                                   10
Pro Ile Val Asp Thr Ser Thr Lys Thr Gly Val
          20
      <210> 152
      <211> 86
      <212> PRT
      <213> mouse
      <400> 152
Met Leu Gln Gly Pro Ala Pro Ser Cys Phe Trp Val Phe Ser Gly Ile
                                   10 ·
1
      5
Cys Val Phe Trp Asp Phe Ile Phe Ile Ile Phe Phe Asn Val Leu Ser
20 25 30
Leu Gly Asn Arg Glu Ile Ser Ala Lys Asp Phe Ala Asp Gln Pro Ala 35 40 45
Gly Ala Gln Gly Met Trp Gly Ile Trp Gly His Thr Ile Thr Cys Gly
```

```
60
                         55
Leu Ala Pro Gly Ala Lys Pro Cys Ser Leu Lys Arg Glu Gly Pro Asp
                   70
Leu Leu Ser Phe Pro Pro
             85
      <210> 153
      <211> 72
      <212> PRT
      <213> mouse
      <400> 153
Met Ser Ala Ile Phe Asn Phe Gln Ser Leu Leu Thr Val Ile Leu Leu 1 5 10 15
Leu Ile Cys Thr Cys Ala Tyr Ile Arg Ser Leu Ala Pro Ser Ile Leu 20 25 30
          20
Asp Arg Asn Lys Thr Gly Leu Leu Gly Ile Phe Trp Lys Cys Ala Arg 35 40 45
Ala Phe Ser Ile Leu Phe Ile Gln
      <210> 154
      <211> 169
<212> PRT
      <213> mouse
      <400> 154
Met Ser Gly Leu Arg Thr Leu Leu Gly Leu Gly Leu Leu Val Ala Gly
                                     10
Ser Arg Leu Pro Arg Val Ile Ser Gln Gln Ser Val Cys Arg Ala Arg
20 25 30
Pro Ile Trp Gly Thr Gln Arg Arg Gly Ser Glu Thr Met Ala Gly 35 40 45
Ala Ala Val Lys Tyr Leu Ser Gln Glu Glu Ala Gln Ala Val Asp Gln 50 55 60
Glu Leu Phe Asn Glu Tyr Gln Phe Ser Val Asp Gln Leu Met Glu Leu
65 70 75 80
Ala Gly Leu Ser Cys Ala Thr Ala Ile Ala Lys Ala Tyr Pro Pro Thr
85 90 95
Ser Met Ser Lys Ser Pro Pro Thr Val Leu Val Ile Cys Gly Pro Gly 100 105 110
Asn Asn Gly Gly Asp Gly Leu Val Cys Ala Arg His Leu Lys Leu Phe
115 120 125
Gly Tyr Gln Pro Thr Ile Tyr Tyr Pro Lys Arg Pro Asn Lys Pro Leu
130 135 140
Phe Thr Gly Leu Val Thr Gln Cys Gln Lys Met Asp Ile Pro Phe Leu
145 150 155 160
Gly Glu Met Pro Pro Glu Asp Gly Met
               165
      <210> 155
      <211> 61
      <212> PRT
```

<213> mouse

PCT/NZ01/00099 WO 01/90357

```
<400> 155
Met Glu Lys Gln Met Asp Ala Ser Val Ser Val Ile Phe Gly Ser Ile
                 5
                                     10
Val Ile Ser Ala Phe Leu Tyr Leu Ser Leu Ala Gly Pro Trp Ala Val
20 25 30
Thr Val Thr Gln Met Arg Thr Ile Ile Ile Thr Met Asp Gln Leu Arg 35 40 45
Asp Ala Leu Ile Leu Asp Glh Leu Lys Val Ala Val Ser
                         55
   50
      <210> 156
      <211> 131
      <212> PRT
      <213> mouse
    · <400> 156
Met Ala Pro Ser Leu Trp Lys Gly Leu Val Gly Val Gly Leu Phe Ala
1
Leu Ala His Ala Ala Phe Ser Ala Ala Gln His Arg Ser Tyr Met Arg
20 25 30
Leu Thr Glu Lys Glu Asp Glu Ser Leu Pro Ile Asp Ile Val Leu Gln
       35
                            40
                                                 45
Thr Leu Leu Ala Phe Ala Val Thr Cys Tyr Gly Ile Val His Ile Ala 50 55 60
Gly Glu Phe Lys Asp Met Asp Ala Thr Ser Glu Leu Lys Asn Lys Thr
65 70 75 80
Phe Asp Thr Leu Arg Asn His Pro Ser Phe Tyr Val Phe Asn His Arg
               85
                                   90
                                                       95
Gly Arg Val Leu Phe Arg Pro Ser Asp Ala Thr Asn Ser Ser Asn Leu
100 105 110
         100
                              105
                                                   110
Asp Ala Leu Ser Ser Asn Thr Ser Leu Lys Leu Arg Lys Phe Asp Ser
      115
                             120
                                                  125
Leu Arg Arg
   130
      <210> 157
      <211> 133
      <212> PRT
      <213> mouse
      <400> 157
Met Arg Leu Leu Ala Ala Ala Leu Leu Leu Leu Leu Leu Ala Leu Cys
                                     10
Ala Ser Arg Val Asp Gly Ser Lys Cys Lys Cys Ser Arg Lys Gly Pro
20 25 30
Lys Ile Arg Tyr Ser Asp Val Lys Lys Leu Glu Met Lys Pro Lys Tyr 35 40 / 45.
Pro His Cys Glu Glu Lys Met Val Ile Val Thr Thr Lys Glu His Val 50 55 60
                        55
Gln Gly Thr Gly Ala Arg Ser Thr Ala Cys Thr Leu Ser Cys Arg Ala 65 70 75 80
Pro Asn Ala Ser Ser Ser Gly Thr Met Pro Gly Thr Arg Ser Ala Gly
85 90 . 95
```

125

90

Ser Thr Lys Asn Arg Val Asp Asp His Gly Lys Lys Asn Ser Arg Pro Val Glu Arg Leu Gln Gln Arg Thr Leu Gln Ile Lys Ile Lys Ala Leu

120

85

```
Ser Phe Ser Gln Ala
130
```

<210> 158 <211> 78

<212> PRT <213> mouse

<210> 159 <211> 206 <212> PRT

<213> mouse

<400> 159 Met Leu Pro Pro Ala Ile His Leu Ser Leu Ile Pro Leu Leu Cys Ile 1 5 10 15 Leu Met Arg Asn Cys Leu Ala Phe Lys Asn Asp Ala Thr Glu Ile Leu 20 25 30 Tyr Ser His Val Val Lys Pro Val Pro Ala His Pro Ser Ser Asn Ser 35 40 45 Thr Leu Asn Gln Ala Arg Asn Gly Gly Arg His Phe Ser Ser Thr Gly 50 55 60 Leu Asp Arg Asn Ser Arg Val Gln Val Gly Cys Arg Glu Leu Arg Ser 65 70 75 80 Thr Lys Tyr Ile Ser Asp Gly Gln Cys Thr Ser Ile Ser Pro Leu Lys 85 90 95 Glu Leu Val Cys Ala Gly Glu Cys Leu Pro Leu Pro Val Leu Pro Asn 100 105 110 Trp Ile Gly Gly Gly Tyr Gly Thr Lys Tyr Trp Ser Arg Arg Ser Ser 115 120 125 Gln Glu Trp Arg Cys Val Asn Asp Lys Thr Arg Thr Gln Arg Ile Gln 130 135 140 Leu Gln Cys Gln Asp Gly Ser Thr Arg Thr Tyr Lys Ile Thr Val Val 145 150 150 160 Thr Ala Cys Lys Cys Lys Arg Tyr Thr Arg Gln His Asn Glu Ser Ser 165 170 175 His Asn Phe Glu Ser Val Ser Pro Ala Lys Pro Ala Gln His His Arg 180 185 190 Glu Arg Lys Arg Ala Ser Lys Ser Ser Lys His Ser Leu Ser 200 195

<210> 160

<211> 169

<212> PRT

<213> mouse

```
<400> 160
Met Ser Gly Leu Arg Thr Leu Leu Gly Leu Gly Leu Leu Val Ala Gly
Ser Arg Leu Pro Arg Val Ile Ser Gln Gln Ser Val Cys Arg Ala Arg
           20.
                                  25
                                                        30
Pro Ile Trp Gly Thr Gln Arg Arg Gly Ser Glu Thr Met Ala Gly 35 40 45
Ala Ala Val Lys Tyr Leu Ser Gln Glu Glu Ala Gln Ala Val Asp Gln 50 55 60
Glu Leu Phe Asn Glu Tyr Gln. Phe Ser Val Asp Gln Leu Met Glu Leu
65 70 75 80
Ala Gly Leu Ser Cys Ala Thr Ala Ile Ala Lys Ala Tyr Pro Pro Thr
85 90 95
Ser Met Ser Lys Ser Pro Pro Thr Val Leu Val Ile Cys Gly Pro Gly
           100
                               105
                                                       110
Asn Asn Gly Gly Asp Gly Leu Val Cys Ala Arg His Leu Lys Leu Phe
115 120 125
Gly Tyr Gln Pro Thr Ile Tyr Tyr Pro Lys Arg Pro Asn Lys Pro Leu
130 135 140
Phe Thr Gly Leu Val Thr Gln Cys Gln Lys Met Asp Ile Pro Phe Leu
145 150 155 160
Gly Glu Met Pro Pro Glu Asp Gly Met
                 165
```

<210> 161

<211> 114

<212> PRT

<213> mouse

<400> 161

Met Ser Val Thr Ile Gly Arg Leu Ala Leu Phe Leu Ile Gly Ile Leu 1 10 15 Leu Cys Pro Val Ala Pro Ser Leu Thr Arg Ser Trp Pro Gly Pro Asp 20 25 30 Thr Cys Ser Leu Phe Leu Gln His Ser Leu Ser Leu Ser Leu Arg Leu 40 35 45 Gly Gln Ser Leu Glu Gly Gly Leu Ser Val Cys Phe His Val Cys Ile 50 55 60 His Ala Cys Glu Cys Val Ala Cys Cys Arg Val Leu Trp Asp Pro Lys 70 Pro Arg Gly Ser Ser Leu Cys Arg Trp Val Leu Gly Ser Ile Thr Cys 90 85 Leu Phe Met Tyr Glu Val Gly Gly Trp Thr Gln Gly Gly Leu Ile Val 100 105 110 Ser Leu

<210> 162

<211> 46

<212> PRT

<213> mouse

<400> 162

Met His Tyr Pro Cys Leu Ala Cys Leu Phe Val Asn Val His Trp Cys

1 5 10 , 15

Phe Ala Trp Met Cys Ile Leu Val Lys Met Ser Glu Leu Leu Glu Leu

```
25
                                                        30
Glu Leu Glu Thr Met Val Ser Cys Leu Val Asp Val Gly Asn
        35
                              40
      <210> 163
      <211> 122
      <212> PRT
      <213> mouse
      <400> 163
Met Phe Thr Phe Val Val Leu Val Ile Thr Ile Val Ile Cys Leu Cys
His Val Cys Phe Gly His Phe Lys Tyr Leu Ser Ala His Asn Tyr Lys
20 25 30
Ile Glu His Thr Glu Thr Asp Ala Val Ser Ser Arg Ser Asn Gly Arg 35 40 45
Pro Pro Thr Ala Gly Ala Val Pro Lys Ser Ala Lys Tyr Ile Ala Gln 50 55 60
Val Leu Gln Asp Ser Glu Gly Asp Gly Asp Gly Asp Gly Ala Pro Gly
65 70 75 80
Ser Ser Gly Asp Glu Pro Pro Ser Ser Ser Ser Gln Asp Glu Glu Leu
85 90 95
Leu Met Pro Pro Asp Gly Leu Thr Asp Thr Asp Phe Gln Ser Cys Glu 100 105 110
Asp Ser Leu Ile Glu Asn Glu Ile His Gln
        115
                             120
      <210> 164
      <211> 60
      <212> PRT
      <213> Rat
      <400> 164
Met Ser Phe Val Lys Ile Glu Ala Thr Pro Thr Gln Thr Lys Trp Pro
Phe Ser Val Val Pro Gln Ser Leu Leu Val Thr Val Tyr Ile Cys Tyr 20 25 30
Ile Phe Leu Val Ile Phe Phe Phe Phe Phe Glu Ala Cys Gln Glu Val 35 40 45
Leu Cys Ser Phe Phe Asp Phe Ser Arg Arg Arg Gly
                         55
      <210> 165
      <211> 57
      <212> PRT
      <213> mouse
      <400> 165
Met Gly Ser Pro Ile Ser Gly Val Cys Pro Val Leu Pro Gly Gly Leu
                                     10
Phe Val Ala Leu Gly Trp Ile Phe Leu Leu Phe His Arg Asp Ala Phe 20 25 30
Ser Leu His Thr Met Ser Ala Gly Phe Pro Lys Ser Pro Ala Asn Pro 35 40 45
His His Pro Pro Leu Arg Leu Ser Pro
50 55
```

```
<210> 166
      <211> 75
      <212> PRT
      <213> mouse
      <400> 166
Lys Thr Arg Arg Thr Leu Thr Gly Gln Leu Gly Leu Phe Ser Val Asp
 1
                                    10
                                                         15
Phe Met Val Cys Ile Phe Leu Phe Leu Phe Phe Cys Phe Leu Phe Pro
20 25 30
Phe Pro Leu Phe Leu Val Arg Lys His Ile Leu Leu Ser His Cys Lys 35 40 45
Gln Trp Glu Gly Ser Thr Met Thr His Thr His Thr His Thr His Ile 50 55 60
His Ile His Thr Pro Pro Arg Gln Cys Gln Ser
65
                    70
      <210> 167
      <211> 52
      <212> PRT
      <213> mouse
      <400> 167
Val Arg Ser Leu Glu Gln Leu Gly Leu Phe Ser Val Asp Phe Met Val
                5
                                    10
Cys Ile Phe Leu Phe Leu Phe Phe Cys Phe Leu Phe Pro Phe Pro Leu 20 25 30
                               25
Phe Leu Val Arg Lys His Ile Leu Leu Ser His Cys Lys Gln Trp Glu
                         . 40
  35
Gly Ser Thr Met
   50
      <210> 168
      <211> 119
      <212> PRT
      <213> Rat
      <400> 168
Met Leu Gly Ala Thr Ser Leu Ser Trp Pro Trp Val Leu Trp Ala Val
                                    10
Ala Gln Arg Asp Ser Val Asp Ala Ile Gly Met Phe Leu Gly Gly Leu 20 25 . 30
Val Ala Thr Ile Phe Leu Asp Ile Ile Tyr Ile Ser Ile Phe Tyr Ser
35 40 45
Ser Val Ala Val Gly Asp Thr Gly Arg Phe Ser Ala Gly Met Ala Ile 50 60 .
Phe Ser Leu Leu Gln Ala Leu Leu Leu Pro Arg Leu Pro His
65 . 70
                                      75
Ala Pro Gly Ser Glu Gly Val Ser Ser Arg Ser Ala Arg Ile Ser Ser 85 90 95
                                   90
Asp Leu Leu Arg Asn Ile Val Pro Thr Arg Gln Leu Thr Arg Gln Thr
His Leu Gln Thr Pro Leu Gln
115
      <210> 169
      <211> 104
```

```
<212> PRT
       <213> Rat
       <220>
       <400> 169
Leu Val Pro Lys Ser Ala Arg Ala Ser Leu Leu Cys Cys Gly Pro Lys
1 5 10 15
Leu Ala Ala Cys Gly Ile Val Leu Ser Ala Trp Gly Val Ile Met Leu
           20
                                 25
Ile Met Leu Gly Ile Phe Phe Asn Val His Ser Ala Val Xaa Ile Xaa
       35
                            40
                                                  45
Asp Val Pro Phe Thr Glu Lys Asp Phe Glu Asn Gly Pro Gln Asn Ile
50 55 60
                       55
                                             60
Tyr Asn Leu Tyr Glu Gln Val Ser Tyr Asn Cys Phe Ile Ala Ala Gly 65 70 75 80
Leu Tyr Leu Leu Xaa Gly Gly Phe Ser Phe Cys Gln Val Arg Leu Asn
        85
Lys Arg Lys Glu Tyr Met Val Arg
     100
      <210> 170
      <211> 123
      <212> PRT
       <213> Rat
      <220>
      <221> UNSURE
      <222> (27)...(27)
      <221> UNSURE
      <222> (104)...(104)
      <221> UNSURE
      <222> (118)...(118)
      <400> 170
Met Arg Pro Gly Ala Asp Trp Ala Ala Val Cys Ala Leu Trp Pro Ser 1 \hspace{1cm} 5 \hspace{1cm} 10 \hspace{1cm} 15
Trp Arg Pro Ser Cys Ser Leu Pro Ser Ser Xaa Arg Ile Gln Pro Asp
20 25 30
                               25
Glu Leu Trp Leu Tyr Arg Asn Pro Tyr Val Lys Ala Glu Tyr Phe Pro 35 40 45
Thr Gly Pro Met Phe Val Ile Ala Phe Leu Thr Pro Leu Ser Leu Ile 50 60
                                             60
Phe Phe Ala Lys Phe Leu Arg Lys Ala Asp Ala Asp Arg Gln Arg Ala 65 . 70 . 75 . 80
Ser Leu Pro Arg Cys Gln Pro Cys Pro Ser Ala Lys Trp Cys Leu Tyr
85 90 95
Gln His His Lys Thr Asp Ser Xaa Gln Gly His Ala Gln Ile Ala Ser
100 105 110
Thr Glu Cys Ser Pro Xaa Gly Ile Ala His Ser
        115
                             120
      <210> 171
      <211> 75
```

> <212> PRT <213> Rat

<400> 171 Ser Ala Gly Val Met Thr Ala Ala Val Phe Phe Gly Cys Ala Phe Ile 10 15 Ala Phe Gly Pro Ala Leu Ser Leu Tyr Val Phe Thr Ile Ala Thr Asp 20 25 30 Pro Leu Arg Val Ile Phe Leu Ile Ala Gly Ala Phe Phe Trp Leu Val 35 40 45 Ser Leu Leu Ser Ser Val Phe Trp Phe Leu Val Arg Val Ile Thr 50 55 60 Asp Asn Arg Asp Gly Pro Val Gln Asn Tyr Leu 70

<210> 172 <211> 79 <212> PRT <213> Human

<400> 172

.

Lys Thr Ser Tyr His Tyr His Thr Asn Val Glu Glu Leu Thr Ile Pro 10 Glu Thr Arg Asn Asn Leu Tyr Ile Ser Ile Ser Trp Leu Trp Cys Leu 25 20 30 Val Leu Val Leu Leu Ser Thr Met Ile Leu Asn Lys His Gly Trp Met 35 40 Lys Ala Asn Ala Tyr Ser Leu Val Pro Ser Ile Ile Tyr Ser Pro Ser 50 55 60 Tyr Leu Lys Leu Leu Leu Arg Leu Tyr Lys Leu Gln Ile Cys Cys 70 75

<210> 173 <211> 134 <212> PRT <213> Human

<220>

<400> 173 Leu Arg Gly Arg Gly Arg Gly Val Cys Ser Gln Glu Ser Phe Gly Gly 10 15 Cys Cys Val Ser Gly Leu Ile Ala Met Gly Thr Lys Ala Gln Val Glu 20 25 30 Arg Lys Leu Cys Leu Phe Ile Leu Ala Ile Leu Leu Cys Ser Leu 35 40 Ala Leu Gly Ser Val Thr Val His Ser Ser Glu Pro Glu Val Arg Ile 50 55 60 Pro Glu Asn Asn Pro Val Lys Leu Ser Cys Ala Tyr Ser Gly Phe Ser 75 70 Ser Pro Arg Val Glu Trp Lys Phe Asp Gln Gly Asp Thr Thr Arg Leu 85 90 95 Val Cys Tyr Asn Asn Lys Ile Thr Ala Ser Tyr Glu Asp Arg Val Thr 100 105 . 110 Phe Leu Pro Thr Gly Ile Thr Phe Lys Ser Val Thr Arg Glu Asp Thr 115 . 120 125 Gly Thr Tyr Thr Cys Met 130

```
<210> 174
      <211> 137
      <212> PRT
      <213> Human
      <400> 174
Ala Trp Ser Arg Pro Arg Tyr Asp Ser Val Leu Ala Leu Ser Ala Ala
 1
                5
                                   10
Leu Gln Ala Thr Arg Ala Leu Met Val Val Ser Leu Val Leu Gly Phe
20 25 30
                               25
                                                  30
Leu Ala Met Phe Val Ala Thr Met Gly Met Lys Cys Thr Arg Cys Gly
       35
                           40
                                              45
Gly Asp Asp Lys Val Lys Lys Ala Arg Ile Ala Met Gly Gly Gly Ile
   50
                      55
                                          60
Ile Phe Ile Val Ala Gly Leu Ala Ala Leu Val Ala Cys Ser Trp Tyr 65 70 75 80
                                      75
Gly His Gln Ile Val Thr Asp Phe Tyr Asn Pro Leu Ile Pro Thr Asn
85 90 95
Ile Lys Tyr Glu Phe Gly Pro Ala Ile Phe Ile Gly Trp Ala Gly Ser 100 105 110
Ala Leu Val Ile Leu Gly Gly Ala Leu Ser Pro Val Pro Val Leu Gly 115 120 125
Ile Arg Ala Gly Leu Gly Thr Cys Pro
                       135
     <210> 175
<211> 43
     <212> PRT
      <213> Human
     <400> 175
Met Lys Leu Ser Gly Met Phe Leu Leu Ser Leu Ala Leu Phe Cys
             5
                        10
Phe Leu Thr Gly Val Phe Ser Gln Gly Gly Gln Val Asp Cys Gly Glu
  20 25
                                                   30
Ser Arg Thr Pro Arg Pro Thr Ala Leu Gly Asn
     35
                           40
     <210> 176
     <211> 63
     <212> PRT
     <213> Rat
     <400> 176
Pro Asn Thr Arg Pro Arg Arg His Thr Ala Cys Arg Val Ser Ile Ser 1 5 10 ... 15
Val Phe Tyr Met Leu His Thr Glu Leu Lys Lys Cys Trp Phe Phe Leu
          20
                             25
                                                 30
Phe Cys Phe Ser Leu Phe Leu Trp Phe Cys Phe Trp Phe Cys Phe Leu 35 40
                                              45
Leu Pro Arg Phe Asp Tyr Leu Pro Met Pro Ser Thr Arg Pro Arg
   50
                       55
     <210> 177
    <211> 52
```

<212> PRT

## <213> mouse <400> 177 Met Leu Gln Gly Pro Ala Pro Ser Cys Phe Trp Val Phe Ser Gly Ile 10 15 Cys Val Phe Trp Asp Phe Ile Phe Ile Ile Phe Phe Asn Val Leu Ser 20 25 30 Leu Gly Asn Arg Glu Ile Ser Ala Lys Asp Phe Ala Asp Gln Pro Ala 40 35 Gly Ala Gln Gly 50 <210> 178 <211> 62 <212> PRT <213> mouse <400> 178 Val Ser Pro Arg Pro Thr Tyr Pro Ser Thr Ala Ser Ser Met Ala Ala 10 Phe Leu Val Thr Gly Phe Phe Phe Ser Leu Phe Val Val Leu Gly Met 20 25 30 Glu Pro Arg Ala Leu Phe Arg Pro Asp Lys Ala Leu Pro Leu Ser Cys 35 40 45 Ala Lys Pro Thr Ser Leu Cys Val Gln Ser Ser Phe Leu Gly 50 60 <210> 179 <211> 123 <212> PRT <213> mouse <400> 179 Ala Ser Arg Thr Ala Val Met Ser Leu Cys Arg Cys Gln Gln Gly Ser 1 5 10 15 Arg Ser Arg Met Asp Leu Asp Val Val Asn Met Phe Val Ile Ala Gly 20 25 30 Gly Thr Leu Ala Ile Pro Ile Leu Ala Phe Val Ala Ser Phe Leu Leu 40 45 Trp Pro Ser Ala Leu Ile Arg Ile Tyr Tyr Trp Tyr Trp Arg Arg Thr 50 55 60 Leu Gly Met Gln Val Arg Tyr Ala His His Glu Asp Tyr Gln Phe Cys 65 70 75 80 Tyr Ser Phe Arg Gly Arg Pro Gly His Lys Pro Ser Ile Leu Met Leu 85 90 95 85 90 His Gly Phe Ser Ala His Lys Gly His Val Ala Gln Arg Gly Gln Val 100 105 Pro Ser Arg Lys Asn Leu His Phe Gly Cys Val 115 120 <210> 180 <211> 120 <212> PRT <213> mouse <220>

<221> UNSURE

<222> (5)...(5)

<400> 180 Ala Arg Arg Arg Xaa Arg Trp Arg Arg Gly Cys Cys Trp Leu Ile Gly 10 Thr Gly Leu Arg Ala Ala Thr Trp Thr Val Leu Cys Ser Pro Asn Ser 25 Ser Leu Val Val Ala Arg His Thr Lys Ser Phe Pro Pro Lys Lys Pro 35 40 45 Leu Gln Ala Leu Thr Met Ser Ile Met Asp His Ser Pro Thr Thr Gly 50 \ 55 60 . Val Val Thr Val Ile Val Ile Leu Ile Ala Ile Ala Ala Leu Gly Gly 70 75 Leu Ile Leu Gly Cys Trp Cys Tyr Leu Arg Leu Gln Arg Ile Ser Gln 85 90 95 Ser Glu Asp Glu Glu Ser Ile Val Gly Asp Gly Glu Thr Lys Glu Pro
100 105 110 Phe Tyr Trp Cys Ser Thr Leu Leu 115

<210> 181 <211> 60 <212> PRT

<213> mouse

<210> 182 <211> 72 <212> PRT <213> mouse

<220>

| Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Valu

<210> 183 <211> 771

<212> PRT <213> Rat

<220>

<400> 183 Glu Leu Tyr Leu Asp Gly Asn Gln Phe Thr Leu Val Pro Lys Glu Leu 5 10 Ser Asn Tyr Lys His Leu Thr Leu Ile Asp Leu Ser Asn Asn Arg Ile 20 - 25 Ser Thr Leu Ser Asn Gln Ser Phe Ser Asn Met Thr Gln Leu Leu Thr 35 . 40 45 Leu Ile Leu Ser Tyr Asn Arg Leu Arg Cys Ile Pro Pro Arg Thr Phe 50 55 60 Asp Gly Leu Lys Ser Leu Arg Leu Leu Ser Leu His Gly Asn Asp Ile 65 70 75 . 80 Ser Val Val Pro Glu Gly Ala Phe Gly Asp Leu Ser Ala Leu Ser His 85 90 95 Leu Ala Ile Gly Ala Asn Pro Leu Tyr Cys Asp Cys Asn Met Gln Trp 100 105 110 Leu Ser Asp Trp Val Lys Ser Glu Tyr Lys Glu Pro Gly Ile Ala Arg 115 120 125 Cys Ala Gly Pro Gly Glu Met Ala Asp Lys Leu Leu Thr Thr Pro 130 135 140 Ser Lys Asn Phe Thr Cys Gln Gly Pro Val Asp Val Thr Ile Gln Ala 145 150 155 160 Lys Cys Asn Pro Cys Leu Ser Asn Pro Cys Lys Asn Asp Gly Thr Cys 165 170 175 Asn Asn Asp Pro Val Asp Phe Tyr Arg Cys Thr Cys Pro Tyr Gly Phe 180 185 190 . Lys Gly Gln Asp Cys Asp Val Pro Ile His Ala Cys Thr Ser Asn Pro 195 200 205 Cys Lys His Gly Gly Thr Cys His Leu Lys Pro Arg Arg Glu Thr Trp 210 215 220 Ile Trp Cys Thr Cys Ala Asp Gly Phe Glu Gly Glu Ser Cys Asp Ile 225 230 235 240 Asn Ile Asp Asp Cys Glu Asp Asn Asp Cys Glu Asn Asn Ser Thr Cys 245 250 255 Val Asp Gly Ile Asn Asn Tyr Thr Cys Leu Cys Pro Pro Glu Tyr Thr 260 265 270 Gly Glu Leu Cys Glu Glu Lys Leu Asp Phe Cys Ala Gln Asp Leu Asn 275 280 285 Pro Cys Gln His Asp Ser Lys Cys Ile Leu Thr Pro Lys Gly Phe Lys 290 295 300 Cys Asp Cys Thr Pro Gly Tyr Ile Gly Glu His Cys Asp Ile Asp Phe 305 310 315 . 320 Asp Asp Cys Gln Asp Asn Lys Cys Lys Asn Gly Ala His Cys Thr Asp 325 330 335 Ala Val Asn Gly Tyr Thr Cys Val Cys Pro Glu Gly Tyr Ser Gly Leu
340 345 350 350 Phe Cys Glu Phe Ser Pro Pro Met Val Phe Leu Arg Thr Ser Pro Cys 355 360 . . . 365 Asp Asn Phe Asp Cys Gln Asn Gly Ala Gln Cys Ile Ile Arg Val Asn 370 375 380 Glu Pro Ile Cys Gln Cys Leu Pro Gly Tyr Leu Gly Glu Lys Cys Glu 390 395

```
Lys Leu Val Ser Val Ser Ile Leu Val Asn Lys Glu Ser Tyr Leu Gln
                   405
                                             410
Ile Pro Ser Ala Lys Val Arg Pro Gln Thr Asn Ile Thr Leu Gln Ile
               420
                                      425
Ala Thr Asp Glu Asp Ser Gly Ile Leu Leu Tyr Lys Gly Asp Lys Asp 435 440 445
His Ile Ala Val Glu Ser Ile Glu Gly Ile Arg Ala Ser Tyr Asp Thr

450 455 460

Gly Ser His Pro Ala Ser Ala Ile Tyr Ser Val Glu Thr Ile Asn Asp

465 470 480
Gly Asn Phe His Ile Val Glu Leu Leu Thr Leu Asp Ser Ser Leu Ser
485 490 495
Leu Ser Val Asp Gly Gly Ser Pro Lys Ile Ile Thr Asn Leu Ser Lys 500 505 510
Gln Ser Thr Leu Asn Phe Asp Ser Pro Leu Tyr Val Gly Gly Met Pro 515 520 525
Gly Lys Asn Asn Val Ala Ser Leu Arg Gln Ala Pro Gly Gln Asn Gly 530 535 540

Thr Ser Phe His Gly Cys Ile Arg Asn Leu Tyr Ile Asn Ser Glu Leu 545 550 555 556
Gln Asp Phe Arg Lys Val Pro Met Gln Thr Gly Ile Leu Pro Gly Cys 565 570 575
Glu Pro Cys His Lys Lys Val Cys Ala His Gly Thr Cys Gln Pro Ser
580 585 590
Ser Gln Ser Gly Phe Thr Cys Glu Cys Glu Glu Gly Trp Met Gly Pro
Leu Cys Asp Gln Arg Thr Asn Asp Pro Cys Leu Gly Asn Lys Cys Val 610 620
His Gly Thr Cys Leu Pro Ile Asn Ala Phe Ser Tyr Ser Cys Lys Cys 625 630 635 640
Leu Glu Gly His Gly Gly Val Leu Cys Asp Glu Glu Glu Asp Leu Phe 645 650 655
Asn Pro Leu Pro Gly Asp Gln Val Gln Ala Arg Glu Val Gln Ala Leu 660 665 670
Trp Ala Arg Ala Ala Leu Leu Trp Met Gln Gln Trp Ile His Arg Gly 675 680 685
Gln Leu Thr Gln Arg Ile Ser Cys Arg Gly Glu Arg Ile Arg Asp Tyr
. 690 695 700
Tyr Gln Ser Ser Arg Val Arg Cys Leu Ser Asn Asp
```

<210> 184

<211> 340

<212> PRT

<213> mouse

<400> 184

Asp Gly Ser Leu Trp Leu Gln Ala Thr Gln Pro Asp Asp Ala Gly His 10 Tyr Thr Cys Val Pro Ser Asn Gly Phe Leu His Pro Pro Ser Ala Ser 20 25 30 Ala Tyr Leu Thr Val Leu Tyr Pro Ala Gln Val Thr Val Met Pro Pro 35 40 Glu Thr Pro Leu Pro Thr Gly Met Arg Gly Val Ile Arg Cys Pro Val 50 55 60 Arg Ala Asn Pro Pro Leu Leu Phe Val Thr Trp Thr Lys Asp Gly Gln 75 70 Ala Leu Gln Leu Asp Lys Phe Pro Gly Trp Ser Leu Gly Pro Glu Gly

Ser Leu Ile Ile Ala Leu Gly Asn Glu Asp Ala Leu Gly Glu Tyr Ser 100 105 110

```
Cys Thr Pro Tyr Asn Ser Leu Gly Thr Ala Gly Pro Ser Pro Val Thr
Arg Val Leu Leu Lys Ala Pro Pro Ala Phe Ile Asp Gln Pro Lys Glu
130 135 140
Glu Tyr Phe Gln Glu Val Gly Arg Glu Leu Leu Ile Pro Cys Ser Ala
145 150 155 160
Arg Gly Asp Pro Pro Pro Ile Val Ser Trp Ala Lys Val Gly Arg Gly 165 170 175
Leu Gln Gly Gln Ala Gln Val Asp Ser Asn Asn Ser Leu Val Leu Arg
180 185 190
Pro Leu Thr Lys Glu Ala Gln Gly Arg Trp Glu Cys Ser Ala Ser Asn
195 200 205
Ala Val Ala Arg Val Thr Thr Ser Thr Asn Val Tyr Val Leu Gly Thr 210 215 220
Ser Pro His Val Val Thr Asn Val Ser Val Val Pro Leu Pro Lys Gly 225 230 235 240
Ala Asn Val Ser Trp Glu Pro Gly Phe Asp Gly Gly Tyr Leu Gln Arg
245 250 255
Phe Ser Val Trp Tyr Thr Pro Leu Ala Lys Arg Pro Asp Arg Ala His 260 265 270
His Asp Trp Val Ser Leu Ala Val Pro Ile Gly Ala Thr His Leu Leu
275 280 285
Val Pro Gly Leu Gln Ala His Ala Gln Tyr Gln Phe Ser Val Leu Ala
290 295 300
Gln Asn Lys Leu Gly Ser Gly Pro Phe Ser Glu Ile Val Leu Ser Ile
305 310 315 320
Pro Glu Gly Leu Pro Thr Thr Pro Ala Ala Pro Gly Leu Pro Ala Thr
                                        330
                325
Arg Ser Arg Val
             340
       <210> 185
       <211> 536
       <212> PRT
       <213> mouse
       <400> 185
Lys Val Glu Gly Glu Gly Arg Gly Arg Trp Ala Leu Gly Leu Leu Arg 1 5 10 15
Thr Phe Asp Ala Gly Glu Phe Ala Gly Trp Glu Lys Val Gly Ser Gly 20 25 30
Gly Phe Gly Gln Val Tyr Lys Val Arg His Val His Trp Lys Thr Trp 35 40 45
Leu Ala Ile Lys Cys Ser Pro Ser Leu His Val Asp Asp Arg Glu Arg 50 55 60
Met Glu Leu Leu Glu Glu Ala Lys Lys Met Glu Met Ala Lys Phe Arg
65 70 75 80
Tyr Ile Leu Pro Val Tyr Gly Ile Cys Gln Glu Pro Val Gly Leu Val
85 90 95
Met Glu Tyr Met Glu Thr Gly Ser Leu Glu Lys Leu Leu Ala Ser Glu
100 105 110
Pro Leu Pro Trp Asp Leu Arg Phe Arg Ile Val His Glu Thr Ala Val
115 120 125
Gly Met Asn Phe Leu His Cys Met Ser Pro Pro Leu Leu His Leu Asp
```

```
135
                                                     140
Leu Lys Pro Ala Asn Ile Leu Leu Asp Ala His Tyr Gln Met Ser Arg
145 150 155 160
Phe Leu Asp Phe Gly Leu Ala Lys Cys Asn Gly Met Ser His Ser His
165 170 175
Asp Leu Ser Met Asp Gly Leu Phe Gly Thr Ile Gly Tyr Leu Pro Pro
180 185 190
Glu Arg Ile Arg Glu Lys Ser Arg Leu Phe Asp Thr Lys His Asp Val
195 200 205
Tyr Ser Phe Ala Ile Val Ile Trp Gly Val Leu Thr Gln Asn Asn Pro
210 215 220
Phe Ala Asp Glu Lys Asn IIe Leu His IIe Met Met Lys Val Val Lys 225 230 235 240
Gly His Arg Pro Glu Leu Pro Pro Ile Cys Arg Pro Arg Pro Arg Ala
245 250 255
Cys Ala Ser Leu Ile Gly Leu Met Gln Arg Cys Trp His Ala Asp Pro
260 265 270
Gln Val Arg Pro Thr Phe Gln Glu Ile Thr Ser Glu Thr Glu Asp Leu
275 280 285
Cys Glu Lys Pro Asp Glu Glu Val Lys Asp Leu Ala His Glu Pro Gly 290 295 300
Glu Lys Ser Ser Leu Glu Ser Lys Ser Glu Ala Arg Pro Glu Ser Ser 305 310 315 320
Arg Leu Lys Arg Ala Ser Ala Pro Pro Phe Asp Asn Asp Cys Ser Leu 325 330 335
Ser Glu Leu Leu Ser Gln Leu Asp Ser Gly Ile Phe Pro Arg Leu Leu
340 345 350
Lys Gly Pro Glu Glu Leu Ser Arg Ser Ser Ser Glu Cys Lys Leu Pro
355 360 365
Ser Ser Ser Ser Gly Lys Arg Leu Ser Gly Val Ser Ser Val Asp Ser 370 375 380 .
Ala Phe Ser Ser Arg Gly Ser Leu Ser Leu Ser Phe Glu Arg Glu Ala
385 390 395 400
Ser Thr Gly Asp Leu Gly Pro Thr Asp Ile Gln Lys Lys Lys Leu Val
405 410 415
Asp Ala Ile Ile Ser Gly Asp Thr Ser Arg Leu Met Lys Ile Leu Gln
420 425 430
Pro Gln Asp Val Asp Leu Val Leu Asp Ser Ser Ala Ser Leu Leu His
435 440 445
Leu Ala Val Glu Ala Gly Gln Glu Glu Cys Val Lys Trp Leu Leu Leu 450 455 460
Asn Asn Ala Asn Pro Asn Leu Thr Asn Arg Lys Gly Ser Thr Pro Leu
465 470 475 480
His Met Ala Val Glu Arg Lys Gly Arg Gly Ile Val Glu Leu Leu Leu 485 490 495
Ala Arg Lys Thr Ser Val Asn Ala Lys Asp Glu Asp Gln Trp Thr Ala 500 505 505
                                                            _, 510
Leu His Phe Ala Ala Gln Asn Gly Asp Glu Gly Gln His Lys Ala Ala 515 520 525
Ala Arg Glu Glu Cys Phe Cys Gln
    530
```

<210> 186

<211> 337

<212> PRT

<213> Rat

<220>

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<400> 186
Arg Phe Gly Tyr Gln Met Asp Glu Gly Asn Gln Cys Val Asp
Val Asp Glu Cys Ala Thr Asp Ser His Gln Cys Asn Pro Thr Gln Ile
             20
Cys Ile Asn Thr Glu Gly Gly Tyr Thr Cys Ser Cys Thr Asp Gly Tyr
        35
                              40
                                                    45
Trp Leu Leu Glu Gly Gln Cys Leu Asp Ile Asp Glu Cys Arg Tyr Gly 50 60
Tyr Cys Gln Gln Leu Cys Ala Asn Val Pro Gly Ser Tyr Ser Cys Thr
65 70 75 80
Cys Asn Pro Gly Phe Thr Leu Asn Asp Asp Gly Arg Ser Cys Gln Asp
85 90 95
Val Asn Glu Cys Glu Thr Glu Asn Pro Cys Val Gln Thr Cys Val Asn 100 105 110
Thr Tyr Gly Ser Phe Ile Cys Arg Cys Asp Pro Gly Tyr Glu Leu Glu
115 120 125
Glu Asp Gly Ile His Cys Ser Asp Met Asp Glu Cys Ser Phe Ser Glu
    130
                          135
                                                140
Phe Leu Cys Gln His Glu Cys Val Asn Gln Pro Gly Ser Tyr Phe Cys
145 150 155 160
Ser Cys Pro Pro Gly Tyr Val Leu Leu Glu Asp Asn Arg Ser Cys Gln
165 170 175
Asp Ile Asn Glu Cys Glu His Arg Asn His Thr Cys Thr Pro Leu Gln 180 185 190
Thr Cys Tyr Asn Leu Gln Gly Gly Phe Lys Cys Ile Asp Pro Ile Val
195 200 205
Cys Glu Glu Pro Tyr Leu Leu Ile Gly Asp Asn Arg Cys Met Cys Pro
210 215 220
Ala Glu Asn Thr Gly Cys Arg Asp Gln Pro Phe Thr Ile Leu Phe Arg
225 230 235 240
                                           235
Asp Met Asp Val Val Ser Gly Arg Ser Val Pro Ala Asp Ile Phe Gln
                245
                                  250
Met Gln Ala Thr Thr Arg Tyr Pro Gly Ala Tyr Tyr Ile Phe Gln Ile
. 260 265 270
Lys Ser Gly Asn Glu Gly Arg Glu Phe Tyr Met Arg Gln Thr Gly Pro
275 280 285
Ile Ser Ala Thr Leu Val Met Thr Arg Pro Ile Lys Gly Pro Arg Asp 290 295 300
Ile Gln Leu Asp Leu Glu Met Ile Thr Val Asn Thr Val Ile Asn Phe
                     310
                                           315
Arg Gly Ser Ser Val Ile Arg Leu Arg Ile Tyr Val Ser Gln Tyr Pro
                  325
                                        330
Phe
```

<210> 187 <211> 152 <212> PRT

<213> mouse

<400> 187
Met Ala Leu Gly Val Leu Ile Ala Val Cys Leu Leu Phe Lys Ala Met
1 5 10 15

```
Lys Ala Ala Leu Ser Glu Glu Ala Glu Val Ile Pro Pro Ser Thr Ala
            20
                               25
                                                  30
Gln Gln Ser Asn Trp Thr Phe Asn Asn Thr Glu Ala Asp Tyr Ile Glu
        35
                           40
                                               45
Glu Pro Val Ala Leu Lys Phe Ser His Pro Cys Leu Glu Asp His Asn
   50
                       55
Ser Tyr Cys Ile Asn Gly Ala Cys Ala Phe His His Glu Leu Lys Gln 65 70 75 80
                    70
Ala Ile Cys Arg Cys Phe Thr Gly Tyr Thr Gly Gln Arg Cys Glu His
               85
                                    90
                                                       95
Leu Thr Leu Thr Ser Tyr Ala Val Asp Ser Tyr Glu Lys Tyr Ile Ala
100 105 110
Ile Gly Ile Gly Val Gly Leu Leu Ile Ser Ala Phe Leu Ala Val Phe
       115
                          120
                                              125
Tyr Cys Tyr Ile Arg Lys Arg Cys Ile Asn Leu Lys Ser Pro Tyr Ile
   130
                       135
                                             140
Ile Cys Ser Gly Gly Ser Pro Leu
145
                    150
      <210> 188
      <211> 118
      <212> PRT
      <213> Rat
      <220>
      <400> 188
Leu Val Pro Gln Phe Gly Thr Arg Ile Arg Tyr ThrAla Tyr Asp Arg
                 5
                                    10
Ala Tyr Asn Arg Ala Ser Cys Lys Phe Ile Val Lys Val Gln Val Arg
          20
                               25
Arg Cys Pro Ile Leu Lys Pro Pro Gln His Gly Tyr Leu Thr Cys Ser 35 40 .45
Ser Ala Gly Asp Asn Tyr Gly Ala Ile Cys Glu Tyr His Cys Asp Gly 50 55 60
Gly Tyr Glu Arg Gln Gly Thr Pro Ser Arg Val Cys Gln Ser Ser Arg 65 70 75 80
```

115 <210> 189

<211> 299

<212> PRT

100 Arg Leu Leu Ile Val Ser

85

<213> Human

<220>

<400> 189

 Met Gly Thr Lys
 Ala Gln Val Glu
 Arg Lys
 Leu Leu Cys
 Leu Leu Cys
 Leu Ala Leu Gly
 Leu Gly
 Ser Val Thr Val His

 Leu Ala Ile
 Leu Leu Cys
 Ser Leu Ala Leu Gly
 Ser Val Thr Val His

 20
 25
 30

 Ser Ser Glu
 Pro Glu Val Arg Ile
 Pro Glu Asn Asn Pro Val Lys
 Leu Leu Leu Leu Cys

Gln Trp Ser Gly Ser Pro Pro Val Cys Thr Pro Met Lys Ile Asn Val

Asn Val Asn Ser Ala Ala Gly Leu Leu Asp Gln Phe Tyr Glu Lys Gln 100 105 110

90

95

```
45
Ser Cys Ala Tyr Ser Gly Phe Ser Ser Pro Arg Val Glu Trp Lys Phe 50 55 60
Asp Gln Gly Asp Thr Thr Arg Leu Val Cys Tyr Asn Asn Lys Ile Thr 65 70 75 80
Ala Ser Tyr Glu Asp Arg Val Thr Phe Leu Pro Thr Gly Ile Thr Phe 85 90 95
Lys Ser Val Thr Arg Glu Asp Thr Gly Thr Tyr Thr Cys Met Val Ser
Glu Glu Gly Gly Asn Ser Tyr Gly Glu Val Lys Val Lys Leu Ile Val
115 120 125
Leu Val Pro Pro Ser Lys Pro Thr Val Asn Ile Pro Ser Ser Ala Thr
130 135 140
Ile Gly Asn Arg Ala Val Leu Thr Cys Ser Glu Gln Asp Gly Ser Pro
145 150 155 160
Pro Ser Glu Tyr Thr Trp Phe Lys Asp Gly Ile Val Met Pro Thr Asn
165 170 175
Pro Lys Ser Thr Arg Ala Phe Ser Asn Ser Ser Tyr Val Leu Asn Pro
180 185 190
Thr Thr Gly Glu Leu Val Phe Asp Pro Leu Ser Ala Ser Asp Thr Gly 195 200 205
Glu Tyr Ser Cys Glu Ala Arg Asn Gly Tyr Gly Thr Pro Met Thr Ser 210 215 220
Asn Ala Val Arg Met Glu Ala Val Glu Arg Asn Val Gly Val Ile Val 225 230 235 240
Ala Ala Val Leu Val Thr Leu Ile Leu Leu Gly Ile Leu Val Phe Gly
245 250 255
Ile Trp Phe Ala Tyr Ser Arg Gly His Phe Asp Arg Thr Lys Lys Gly 260 265 270
Thr Ser Ser Lys Lys Val Ile Tyr Ser Gln Pro Ser Ala Arg Ser Glu
275 280 285
Gly Glu Phe Lys Gln Thr Ser Ser Phe Leu Val
   290
                           295
      <210> 190
       <211> 91
       <212> PRT
      <213> Human
      <400> 190
Gln Pro Thr Val Phe Trp Pro Lys Thr Ser Ala Lys Lys Gly Asn Trp 1 5 10 15.
Val Leu Arg Leu Gly Leu Ser Asn Pro Asp Arg Pro Ala Arg Gln Asn 20 25 30
                                                         30
Asn Trp Phe Leu Pro Ala Ser Arg Glu Ile Pro Glu His Ser Ala Leu
35 40 45
                            40
                                                 45
Thr Arg Tyr Pro Ala Gln Ile Arg Gly Cys Trp Pro His Arg Leu Thr 50 55 60
Lys Pro Gln Thr Cys Leu Pro Gln Ala Arg Ser Tyr Leu Ser His Glu
65 70 75 80
Val Thr Gln Ala Thr Arg Thr Cys Pro Gly Gly
```

85

<210> 191 <211> 89 <212> PRT <213> mouse 90

> <210> 192 <211> 299 <212> PRT <213> mouse

<220> ·

<400> 192 Ala Arg Ala Gly Ala Cys Tyr Cys Pro Ala Gly Phe Leu Gly Ala Asp 1  $\phantom{-}$  5  $\phantom{-}$  10  $\phantom{-}$  15  $\phantom{-}$  . Cys Ser Leu Ala Cys Pro Gln Gly Arg Phe Gly Pro Ser Cys Ala His 20 25 30 Val Cys Thr Cys Gly Gln Gly Ala Ala Cys Asp Pro Val Ser Gly Thr 35 40 . 45 Cys Ile Cys Pro Pro Gly Lys Thr Gly Gly His Cys Glu Arg Gly Cys 50 55 60 Pro Gln Asp Arg Phe Gly Lys Gly Cys Glu His Lys Cys Ala Cys Arg 65 70 75 80 Asn Gly Gly Leu Cys His Ala Thr Asn Gly Ser Cys Ser Cys Pro Leu 85 90 95 Gly Trp Met Gly Pro His Cys Glu His Ala Cys Pro Ala Gly Arg Tyr . 100 105 110 Gly Ala Ala Cys Leu Leu Glu Cys Ser Cys Gln Asn Asn Gly Ser Cys 115 120 125 Glu Pro Thr Ser Gly Ala Cys Leu Cys Gly Pro Gly Phe Tyr Gly Gln 130 135 140 Ala Cys Glu Asp Thr Cys Pro Ala Gly Phe His Gly Ser Gly Cys Gln 145 150 155 160 Arg Val Cys Glu Cys Gln Gln Gly Ala Pro Cys Asp Pro Val Ser Gly 165 170 175 Arg Cys Leu Cys Pro Ala Gly Phe Arg Gly Gln Phe Cys Glu Arg Gly 180 185 190 Cys Lys Pro Gly Phe Phe Gly Asp Gly Cys Leu Gln Gln Cys Asn Cys 195 200 205 Pro Thr Gly Val Pro Cys Asp Pro Ile Ser Gly Leu Cys Leu Cys Pro 210 215 220 Pro Gly Arg Ala Gly Thr Thr Cys Asp Leu Asp Cys Arg Arg Gly Arg 225 230 235 240 Phe Gly Pro Gly Cys Ala Leu Arg Cys Asp Cys Gly Gly Gly Ala Asp 245 250 255 Cys Asp Pro Ile Ser Gly Gln Cys His Cys Val Asp Ser Tyr Thr Gly

```
260
                                     265
Pro Thr Cys Arg Glu Val Pro Thr Gln Leu Ser Ser Ile Arg Pro Ala
        275
                            280
                                                        285
Pro Gln His Ser Ser Ser Lys Ala Met Lys His
    290
       <210> 193
<211> 314
       <212> PRT
       <213> mouse
       <220>
               <400> 193
Glu Glu Pro Cys Asn Asn Gly Ser Glu Ile Leu Ala Tyr Asn Ile Asp
                                         10
Leu Gly Asp Ser Cys Ile Thr Val Gly Asn Thr Thr Thr His Val Met 20 25 30
Lys Asn Leu Leu Pro Glu Thr Thr Tyr Arg Ile Arg Ile Gln Ala Ile 35 40 45
Asn Glu Ile Gly Val Gly Pro Phe Ser Gln Phe Ile Lys Ala Lys Thr 50 55 60
Arg Pro Leu Pro Pro Ser Pro Pro Arg Leu Glu Cys Ala Ala Ser Gly 65 70 75 80
Pro Gln Ser Leu Lys Leu Lys Trp Gly Asp Ser Asn Ser Lys Thr His
Ala Ala Gly Asp Met Val Tyr Thr Leu Gln Leu Glu Asp Arg Asn Lys
100 105 110
Arg Phe Ile Ser Ile Tyr Arg Gly Pro Ser His Thr Tyr Lys Val Gln
115 120 125
Arg Leu Thr Glu Phe Thr Cys Tyr Ser Phe Arg Ile Gln Ala Met Ser 130 135 140

Glu Ala Gly Glu Gly Pro Tyr Ser Glu Thr Tyr Thr Phe Ser Thr Thr 145 150 155 160
Lys Ser Val Pro Pro Thr Leu Lys Ala Pro Arg Val Thr Gln Leu Glu
165 170 175
Gly Asn Ser Cys Glu Ile Phe Trp Glu Thr Val Pro Pro Met Arg Gly
180 185 190
Asp Pro Val Ser Tyr Val Leu Gln Val Leu Val Gly Arg Asp Ser Glu
195 200 205
Tyr Lys Gln Val Tyr Lys Gly Glu Glu Ala Thr Phe Gln Ile Ser Gly 210 215 220
Leu Glm Ser Asn Thr Asp Tyr Arg Phe Arg Val Cys Ala Cys Arg Arg
225 230 235 240
Cys Val Asp Thr SerGln Glu Leu Ser Gly Ala Phe Ser Pro Ser Ala
245 250 255
Ala Phe Met Leu Gln Gln Arg Glu Val Met Leu Thr Gly Asp Leu Gly 260 265 , 270
Gly Met Glu Glu Ala Lys Met Lys Gly Met Met Pro Thr Asp Glu Gln
275 280 285
Phe Ala Ala Leu Ile Val Leu Gly Phe Ala Thr Leu Ser Ile Leu Phe
    290
                          295
                                                    300
Ala Phe Ile Leu Gln Tyr Phe Leu Met Lys
       <210> 194
       <211> 109
       <212> PRT
```

## <213> mouse

 <400>
 194

 Gly Thr Arg Val
 Gly Thr Pro Tyr Tyr Met Ser Pro Glu Arg Ile His 1
 15

 Glu Asn Gly Tyr Sar Phe Lys Ser Asp Ile Trp Ser Leu Gly Cys Leu 20
 25

 Leu Tyr Glu Met Ala Ala Leu Gln Ser Pro Phe Tyr Gly Asp Lys Met 35
 40

 Asn Leu Tyr Ser Leu Cys Lys Lys Ile Glu Gln Cys Asp Tyr Pro Pro 50
 55

 Leu Pro Ser Asp His Tyr Ser Glu Glu Leu Arg Gln Leu Val Asn Ile 65
 70

 Cys Ile Asn Pro Asp Pro Glu Lys Arg Pro Asp Ile Ala Tyr Val Tyr 90
 95

 Asp Val Ala Lys Arg Met His Ala Cys Thr Ala Ser Thr

<210> 195 <211> 237 <212> PRT

<213> mouse <400> 195

Met Leu Ser Leu Arg Ser Leu Leu Pro His Leu Gly Leu Phe Leu Cys Leu Ala Leu His Leu Ser Pro Ser Leu Ser Ala Ser Asp Asn Gly Ser 20 25 30 Cys Val Val Leu Asp Asn Ile Tyr Thr Ser Asp Ile Leu Glu Ile Ser 35 40 45 Thr Met Ala Asn Val Ser Gly Gly Asp Val Thr Tyr Thr Val Thr Val 50 55 60 Pro Val Asn Asp Ser Val Ser Ala Val Ile Leu Lys Ala Val Lys Glu 65 70 75 80 Asp Asp Ser Pro Val Gly Thr Trp Ser Gly Thr Tyr Glu Lys Cys Asn 85 90 95 Asp Ser Ser Val Tyr Tyr Asn Leu Thr Ser Gln Ser Gln Ser Val Phe . 100 105 110 100 Gln Thr Asn Trp Thr Val Pro Thr Ser Glu Asp Val Thr Lys Val Asn 115 120 125 Leu Gln Val Leu Ile Val Val Asn Arg Thr Ala Ser Lys Ser Ser Val 130 135 140 Lys Met Glu Gln Val Gln Pro Ser Ala Ser Thr Pro Ile Pro Glu Ser 145 150 155 160 Ser Glu Thr Ser Gln Thr Ile Asn Thr Thr Pro Thr Val Asn Thr Ala 165 170 175 Lys Thr Thr Ala Lys Asp Thr Ala Asn Thr Thr Ala Val Thr Thr Ala 180 185 190 Asn Thr Thr Ala Asn Thr Thr Ala Val Thr Thr Ala Lys Thr Thr Ala 195 200 205 Lys Ser Leu Ala Ile Arg Thr Leu Gly Ser Pro Leu Ala Gly Ala Leu 215 220 His Ile Leu Leu Val Phe Leu Ile Ser Lys Leu Leu Phe 230

<210> 196 <211> 154

<212> PRT <213> Human

<400> 196 Met Ala Leu Gly Val Pro Ile Ser Val Tyr Leu Leu Phe Asn Ala Met 10 Thr Ala Leu Thr Glu Glu Ala Ala Val Thr Val Thr Pro Pro Ile Thr 20 ٠ 25 30 Ala Gln Gln Gly Asn Trp Thr Val Asn Lys Thr Glu Ala His Asn Ile 40 35 Glu Gly Pro Ile Ala Leu Lys Phe Ser His Leu Cys Leu Glu Asp His 50 55 60 50 Asn Ser Tyr Cys Ile Asn Gly Ala Cys Ala Phe His His Glu Leu Glu 75 **70** . Lys Ala Ile Cys Arg Cys Phe Thr Gly Tyr Thr Gly Glu Arg Cys Glu 85 90 95 His Leu Thr Leu Thr Ser Tyr Ala Val Asp Ser Tyr Glu Lys Tyr Ile 100 105 110 100 Ala Ile Gly Ile Gly Val Gly Leu Leu Leu Ser Gly Phe Leu Val Ile 115 120 125 Phe Tyr Cys Tyr Ile Arg Lys Arg Cys Leu Lys Leu Lys Ser Pro Tyr 130 135 140 Asn Val Cys Ser Gly Glu Arg Arg Pro Leu · 150 145

> <210> 197 <211> 171 <212> PRT

<213> Rat

<400> 197 Met Ala Arg Pro Ala Pro Trp Trp Leu Arg Pro Leu Ala Ala Leu 10 Ala Leu Ala Leu Val Arg Val Pro Ser Ala Arg Ala Gly Gln 20 25 30 Met Pro Arg Pro Ala Glu Arg Gly Pro Pro Val Arg Leu Phe Thr Glu 35 40 45 Glu Glu Leu Ala Arg Tyr Ser Gly Glu Glu Glu Asp Gln Pro Ile Tyr 50 55 60 Leu Ala Val Lys Gly Val Val Phe Asp Val Thr Ser Gly Lys Glu Phe 65 70 75 80 Tyr Gly Arg Gly Ala Pro Tyr Asn Ala Leu Ala Gly Lys Asp Ser Ser 90 95 85 90 Arg Gly Val Ala Lys Met Ser Leu Asp Pro Ala Asp Leu Thr His Asp 100 105 110 Ile Ser Gly Leu Thr Ala Lys Glu Leu Glu Ala Leu Asp Asp Ile Phe 125 120 115 Ser Lys Val Tyr Lys Ala Lys Tyr Pro Ile Val Gly Tyr Thr Ala Arg 130 135 140 Arg Ile Leu Asn Glu Asp Gly Ser Pro Asn Leu Asp Phe Lys Pro Glu 145 \* 150 155 160 Asp Gln Pro His Phe Asp Ile Lys Asp Glu Phe 165

<210> 198 <211> 1399 <212> DNA

## <213> Mouse

```
<400> 198
ggcaaagact teggcacgag asaacagcaa agcagagctg gctgcagcca ttcactggcc
tcgggcgggc gtgccacaga ggcagttgaa gtgaaagtga aagagaaacg ataagagaac
                                                                      120
ggagaccaca ggtgctaagt gagggtgctc acagaacccc ctcttcagcc agagatcact
                                                                      180
agcaggggaa ctgtggagaa ggcagccagc aaggaagagc ctgagagtag cctccatggg
                                                                      240
cttggagecc agetggtate tgetgetetg tttggetgte tetggggeag eagggaetga
                                                                      300
ccctcccaca gcgcccacca cagcagaaag acagcggcag cccacggaca tcatcttaga
                                                                      360
                                                                       420
ctgcttcttg gtgacagaag acaggcaccg cggggctttt gccagcagtg gggacaggga
gagggccttg cttgtgctga agcaggtacc agtgctggat gatggctccc tggaaggcat
                                                                       480
cacagattte caggggagca etgagaccaa acaggattea cetgttatet ttgaggeete
                                                                       540
agtggacttg gtacagatte cccaggcaga ggcgttgcte catgctgact gcagcgggaa
                                                                       600
ggcagtgacc tgcgagatct ccaagtattt cctccaggcc agacaagagg ccacttttga
                                                                       660
gaaagcacat tggttcatca gcaacatgca ggtttctaga ggtggcccca gtgtctccat
                                                                       720
                                                                       780
ggtgatgaag actctaagag atgctgaagt tggagctgtc cggcacccta cactgaacct
acctctgagt gcccagggca cagtgaagac tcaagtggag ttccaggtga catcagagac
                                                                       840
ccaaaccetg aaccacetge tggggtcctc tgtctccctg cactgcagtt tctccatggc
                                                                       900
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                                                                       960
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1440

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1560

1620

1680

1740

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## <213> Mouse

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cttacctgat gecettete etcaatcaga gtggateeet tetetactae ttgactttgg
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catcaacaga tetgacgtta getgtgeeca tetgeaacte tetggeeate gtetttacae
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caaatgtgcc acacgctcgc tcttttttac acccagtgcc tctgactctg tccccatggg
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egeoggtgee ttettetaat tagtgtetet getgettteg tetgttttet ggtteetagt
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95

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Asp Arg His Arg Gly Ala Phè Ala Ser Ser Gly Asp Arg Glu Arg Ala 50 55 60
Leu Leu Val Leu Lys Gln Val Pro Val Leu Asp Asp Gly Ser Leu Glu 65 70 75 80
Gly Ile Thr Asp Phe Gln Gly Ser Thr Glu Thr Lys Gln Asp Ser Pro
85 90 95
Val Ile Phe Glu Ala Ser Val Asp Leu Val Gln Ile Pro Gln Ala Glu
100 105 110
Ala Leu Leu His Ala Asp Cys Ser Gly Lys Ala Val Thr Cys Glu Ile
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Ser Lys Tyr Phe Leu Gln Ala Arg Gln Glu Ala Thr Phe Glu Lys Ala
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Ser Met Val Met Lys Thr Leu Arg Asp Ala Glu Val Gly Ala Val Arg
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His Pro Thr Leu Asn Leu Pro Leu Ser Ala Gln Gly Thr Val Lys Thr
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Gln Ile Ser Thr Ser Leu Tyr Gln Ala Gln Gln Ile Met Pro Leu Asn
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Leu Ile Arg Tyr Gly Lys Thr Lys Gln Ser Gly Ser Arg Arg Pro Ala 50 60
Val Cys Arg Ala Phe Asp Val Pro Lys Arg Tyr Phe Ser His Phe Tyr
65 70 75 80
Val Val Ser Val Leu Trp Asn Gly Ser Leu Leu Trp Phe Leu Ser Gln
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Tyr Val Ser Val Phe Ser Asn Thr Ala Ile His Val Val Gln Tyr Cys
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Phe Gly Leu Val Tyr Tyr Val Leu Val Gly Leu Thr Val Leu Ser Gln
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Phe Thr Gly Leu Val Thr Gln Cys Gln Lys Met Asp Ile Pro Phe Leu
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<212> PRT

<213> Mouse

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PCT/NZ01/00099

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<210> 289 <211> 46 <212> PRT <213> Mouse

Ser Leu

<210> 290 <211> 199 <212> PRT <213> Mouse

Gly Phe Cys Gln Leu Ser Gln Leu Ala Ser Ala Asp Pro Glu Arg Arg 55 Ser Pro Arg Ala Ile Val Pro Arg Ala Pro Arg Pro Arg Ser Arg Arg 65 70 75 80 70 Arg Pro Cys Leu Pro Gly Phe Ser Arg Arg Phe Pro Arg Glu Arg Arg 85 90 95 Ser Pro Gly Gln Pro Pro Ser Arg Thr Pro Gln Pro Pro Gln Pro Cys 100 105 110 100 Arg Gly Pro Ser Pro Gly Thr Ala Gln Thr Arg Ser Asn Leu Arg Gly 120 Trp Gln Arg Gly Gly Ser Ile Val Leu Gln Ala Ser Glu Arg Thr Arg 135 140 Ala Gly Cys Arg Thr Pro Val Cys Val Ser His Pro Ser Ala Phe Pro 145 150 155 160 Pro Pro Arg Ala Leu Phe Gly Val Phe Val Ala Ser Ala Pro Glu Val 170 165 Val Cys Val Cys Val Ser Val Val Leu Ser Val Cys Leu Leu Ser Pro 180 185 190 Arg Gly Lys Thr Leu Val Asp 195

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Pro Lys Pro Gly Leu Asp Phe Ser Pro Phe Asp Phe Ala His Phe Gly 245 250 255
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Phe Pro Thr Asp Asn Leu Gly Lys Asp Arg Ser Phe Leu Ala Lys Pro
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Ser Pro Lys Val Gly Arg His Val Tyr Trp Arg Pro Lys Val Asp Ile
275 280 285
Lys Lys Ile Cys Ile Gly Ser Lys Asn Ile Phe Thr Val Ser Asp Leu
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Lys Pro Asn Thr Gln Tyr Tyr Phe Asp Val Phe Met Val Asn Thr Asn 305 310 315 320
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Thr Asn Met Asn Thr Ala Phe Val Gly Ala Phe Ala Arg Thr Lys Glu 325 330 335
Glu Ala Lys Gln Lys Thr Val Glu Leu Lys Asp Gly Arg Val Thr Asp 340 345 350
Val Val Val Lys Arg Lys Gly Lys Lys Phe Leu Arg Phe Ala Pro Val 355 360 365
Ser Ser His Gln Lys Val Thr Leu Phe Ile His Ser Cys Met Asp Thr
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Val Gln Val Gln Val Arg Arg Asp Gly Lys Leu Leu Ser Gln Asn
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Val Glu Gly Ile Arg Gln Phe Gln Leu Arg Gly Lys Pro Lys Gly Lys
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Tyr Leu Ile Arg Leu Lys Gly Asn Lys Lys Gly Ala Ser Met Leu Lys
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Ile Leu Ala Thr Thr Arg Pro Ser Lys His Ala Phe Pro Ser Leu Pro 435 440 445
Asp Asp Thr Arg Ile Lys Ala Phe Asp Lys Leu Arg Thr Cys Ser Ser 450 455 460
Val Thr Val Ala Trp Leu Gly Thr Glu Glu Arg Arg Lys Phe Cys Ile 465 470 475 480
Tyr Arg Lys Glu Val Gly Gly Asn Tyr Ser Glu Glu Gln Lys Arg Arg
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Glu Arg Asn Gln Cys Leu Gly Pro Asp Thr Arg Lys Lys Ser Glu Lys
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Val Leu Cys Lys Tyr Phe His Ser Gln Asn Leu Gln Lys Ala Val Thr
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Thr Glu Thr Ile Arg Asp Leu Gln Pro Gly Lys Ser Tyr Leu Leu Asp
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Val Tyr Val Val Gly His Gly Gly His Ser Val Lys Tyr Gln Ser Lys 545
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Leu Val Lys Thr Arg Lys Val Cys
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<211> 123

<212> PRT

<213> Mouse

<400> 292

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115 120 125 His Gly Ile Pro Gly Lys Lys Gly Pro Lys Gly Lys Lys Gly Glu Pro 130 135 140 Gly Leu Pro Gly Pro Cys Ser Cys Gly Ser Ser Arg Ala Lys Ser Ala 145 150 155 160 Phe Ser Val Ala Val Thr Lys Ser Tyr Pro Arg Glu Arg Leu Pro Ile 170 165 175 Lys Phe Asp Lys Ile Leu Met Asn Glu Gly Gly His Tyr Asn Ala Ser 180 185

Ser Gly Lys Phe Val Cys Ser Val Pro Gly Ile Tyr Tyr Phe Thr Tyr 195 200 205 Asp Ile Thr Leu Ala Asn Lys His Leu Ala Ile Gly Leu Val His Asn 210 215 220 Gly Gln Tyr Arg Ile Arg Thr Phe Asp Ala Asn Thr Gly Asn His Asp 225 230 235 240 225 235 Val Ala Ser Gly Ser Thr Ile Leu Ala Leu Lys Glu Gly Asp Glu Val 245 250 255 245 250 Trp Leu Gln Ile Phe Tyr Ser Glu Gln Asn Gly Leu Phe Tyr Asp Pro Tyr Trp Thr Asp Ser Leu Phe Thr Gly Phe Leu Ile Tyr Ala Asp Gln 275 280 285 Gly Asp Pro Asn Glu Val 290

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<210> 296 <211> 444 <212> PRT



<213> Rat

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<212> PRT

<213> Human

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35 45 Leu Asp Val Gly Leu Ser Asn Trp Ser Phe Leu Tyr Val Thr Val Ser 60

55 50

Leu 65

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<213> Human

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Cys Val Leu Gly Leu Lys Phe Lys Phe 35 40

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<212> PRT

<213> Mouse

<400> 300

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25 Phe Arg Phe Cys Cys Ser Pro Trp Ser Gln His Phe Gly Cys Gly Arg 35 40 45 Leu Thr Ser Cys Leu Pro Pro Cys Val Asp Arg Val Val Lys Thr Tyr 55 60 Ser Ser Pro Pro Cys Leu Ser Val Asn Gly His Asp Val Thr Ile Cys 65 ، 70 75

<210> 301

<211> 82

<212> PRT

<213> Mouse

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Val Val Glu Val Trp Ser Gln Leu Leu Ser Gln Lys His Val Gly Leu 195 200 205 Ile His Met Leu Thr His Leu Ala Glu Ala Leu His Gln Ala Arg Leu 210 215 220 Leu Val Ile Leu Val Ile Pro Pro Ala Val Thr Pro Gly Thr Asp Gln 225 230 235 Leu Gly Met Phe Thr His Lys Glu Phe Glu Gln Leu Ala Pro Ile Leu 245 250 255 Asp Gly Phe Ser Leu Met Thr Tyr Asp Tyr Ser Thr Ser Gln Gln Pro 260 265 270 Gly Pro Asn Ala Pro Leu Ser Trp Ile Arg Ala Cys Val Gln Val Leu 275 280 285 Asp Pro Lys Ser Gln Trp Arg Ser Lys Ile Leu Leu Gly Leu Asn Phe 290 295 300 Tyr Gly Met Asp Tyr Ala Ala Ser Lys Asp Ala Arg Glu Pro Val Ile 310 315 Gly Ala Arg Ala Val Leu Lys Val Ala Leu Pro Leu Ala Val Ser Ser 325 330 335 Gln Gln Ile Trp Thr Leu Gly Arg Gly Gly Ser Thr Ser Ala Leu Leu 340 345 350 Leu Ala Gly Leu Gly Leu Ala Ser Glu Pro Cys Thr Lys Ser Glu Glu 355 360 365 Val Pro Lys Lys Ser Leu Leu Asp Thr Val Trp His Trp Gln Gly Glu 370 375 380 Pro Gly Ala Leu Cys Arg Gly Arg Leu His Thr Trp Ile Leu Val Ser 390 395 Ala Val Pro Gln Ala Cys Thr Cys Leu Phe Gln 405

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Ser	Pro	Phe	Asp 180	Thr	Gln	Lys	Ile	Val 185	Ser	Gly	Gly	His	Thr 190	Val	qaA
Leu	Pro	Tyr 195	Glu	Phe	Leu	Leu	Pro 200	Cys	Met	Cys	Ile	Glu 205	Ala	Ser	Tyr
. Leu	Gln 210	Glu	Asp	Thr	Val	Arg 215	Arg	Lys	Lys	Сув	Pro 220	Phe	Gln	Ser	Trp
225			_		230	•				235		Arg			240
	•			245					250			Leu		255	
	-		260					265			_	Pro	270		
ā		275					280					Glu 285	_	_	_
	290					295					300	Phe			
305		,			310			_		315		Ser			320
				325			_		330			Gln		335	
			340					345				Ala	350		
	_	355	_		_		360					Tyr 365			
	370					375					380	Ile			
385					390					395		Asp			400
		-		405		_			410			Tyr -		415	
			420			•		425				Pro	430		
		435	•	_		•	440					Val 445			
	450			_		455					460	Asp			
465		-		_	470				_	475	_	Pro			480
				485		_			490			Gly		495	
			500	_				505			-	Ser	510		
		515					520					Pro 525			
	530					535					540	Asp			
545				•	550					555		Asp			560
		_		565	_				570			Ala		575	
			580					585				Leu	590		
		595					600		Asp	ASP	īyr	<b>Gln</b> 605	GTĀ	ser	Thr
asn	5er 610	.hto	Сув	GIÅ	hue	5er 615	Cys	ren							

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100 105 110 Glu Asn Asn Tle Arg Thr Ile Thr Tyr Asp Ser Leu Ser Lys Ile Pro 115 120 125 Tyr Leu Glu Glu Leu His Leu Asp Asp Asn Ser Val Ser Ala Val Ser 130 135 140 Ile Glu Glu Gly Ala Phe Arg Asp Ser Asn Tyr Leu Arg Leu Leu Phe 145 150 150 155 160 Leu Ser Arg Asn His Leu Ser Thr Ile Pro Gly Gly Leu Pro Arg Thr 165 170 175 170 Ile Glu Glu Leu Arg Leu Asp Asp Asn Arg Ile Ser Thr Ile Ser Ser 180 185 . 190 Pro Ser Leu His Gly Leu Thr Ser Leu Lys Arg Leu Val Leu Asp Gly 195 200 205 200 Asn Leu Leu Asn Asn His Gly Leu Gly Asp Lys Val Phe Phe Asn Leu 210 215 220 Val Asn Leu Thr Glu Leu Ser Leu Val Arg Asn Ser Leu Thr Ala Ala 225 230 235 240 Pro Val Asn Leu Pro Gly Thr Ser Leu Arg Lys Leu Tyr Leu Gln Asp 245 250 255 Asn His Ile Asn Arg Val Pro Pro Asn Ala Phe Ser Tyr Leu Arg Gln 260 265

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Leu Tyr Arg Leu Asp Met Ser Asn Asn Leu Ser Asn Leu Pro Gln
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                               280
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Gly Ile Phe Asp Asp Leu Asp Asn Ile Thr Gln Leu Ile Leu Arg Asn
    290
                         295
                                                 300
Asn Pro Trp Tyr Cys Gly Cys Lys Met Lys Trp Val Arg Asp Trp Leu
305 310 315 320
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Gln Ser Leu Pro Val Lys Val Asn Val Arg Gly Leu Met Cys Gln Ala
325 330 335
Pro Glu Lys Val Arg Gly Met Ala Ile Lys Asp Leu Ser Ala Glu Leu 340 345 350
Phe Asp Cys Lys Asp Ser Gly Ile Val Ser Thr Ile Gln Ile Thr Thr 355 360 365
Ala Ile Pro Asn Thr Ala Tyr Pro Ala Gln Gly Gln Trp Pro Ala Pro 370 375 . 380
Val Thr Lys Gln Pro Asp Ile Lys Asn Pro Lys Leu Ile Lys Asp Gln
385 390 395 400
Arg Thr Thr Gly Ser Pro Ser Arg Lys Thr Ile Leu Ile Thr Val Lys
405 410 415
Ser Val Thr Pro Asp Thr Ile His Ile Ser Trp Arg Leu Ala Leu Pro 420 425 430
Met Thr Ala Leu Arg Leu Ser Trp Leu Lys Leu Gly His Ser Pro Ala 435 440 445
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Phe Gly Ser Ile Thr Glu Thr Ile Val Thr Gly Glu Arg Ser Glu Tyr 450 455 460
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485 490 . 495
Ile Glu Thr Gln Thr Ala Pro Leu Arg Met Tyr Asn Pro Thr Thr Thr 500 505 510
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Leu Asn Arg Glu Glu Glu Lys Glu Pro Tyr Lys Asn Pro Asn Leu Pro 515 520 525
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Leu Ala Ala Ile Ile Gly Gly Ala Val Ala Leu Val Ser Ile Ala Leu 530 535 540
Leu Ala Leu Val Cys Trp Tyr Val His Arg Asn Gly Ser Leu Phe Ser 545 550 555 560
Arg Asn Cys Ala Tyr Ser Lys Gly Arg Arg Arg Lys Asp Asp Tyr Ala
565 570 575
Glu Ala Gly Thr Lys Lys Asp Asn Ser Ile Leu Glu Ile Arg Glu Thr
580 585 590
Ser Phe Gln Met Leu Pro Ile Ser Asn Glu Pro Ile Ser Lys Glu Glu
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Phe Val Ile His Thr Ile Phe Pro Pro Asn Gly Met Asn Leu Tyr Lys 610 615 620
Asn Asn Leu Ser Glu Ser Ser Ser Asn Arg Ser Tyr Arg Asp Ser Gly
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Ile Pro Asp Ser Asp His Ser His Ser
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<212> PRT

<213> Rat

<400> 306

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<213> Rat

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100 105 110 Glu Leu Trp Val Trp Phe Gln Asp Thr Val Thr Asp Val Asp Lys Ser 115 120 125 Trp Lys Glu Leu Ser Asn Val Leu Ser Gly Ile Phe Cys Ala Ser Leu
130 135 140 140 Asn Phe Ile Asp Ser Thr Asn Thr Val Thr Pro Thr Ala Ser Phe Lys 150 155 Pro Leu Gly Leu Ala Asn Asp Thr Asp His Tyr Phe Leu Arg Tyr Ala 165 170 . 175 Val Leu Pro Arg Glu Val Val Cys Thr Glu Asn Leu Thr Pro Trp Lys 180 185 190 Lys Leu Leu Pro Cys Ser Ser Lys Ala Gly Leu Ser Val Leu Leu Lys 195 200 205 Ala Asp Arg Leu Phe His Thr Ser Tyr His Ser Gln Ala Val His Ile 210 215 220 Arg Pro Ile Cys Arg Asn Ala His Cys Thr Ser Ile Ser Trp Glu Leu 230 235 Arg Gln Thr Leu Ser Val Val Phe Asp Ala Phe Ile Thr Gly Gln Gly . 250

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Lys Lys Asp Trp Ser Leu Phe Arg Met Phe Ser Arg Thr Leu Thr Glu
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                                               285
Tyr Ser Gln Asp Asn Glu Thr Leu Glu Val Ser Pro Pro Pro Thr Ser
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                                           300
Thr Tyr Gln Asp Val Ile Leu Gly Thr Arg Lys Thr Tyr Ala Val Tyr
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                                       315
                                                            320
Asp Leu Phe Asp Thr Ala Met Ile Asn Asn Ser Arg Asn Leu Asn Ile 325 330 335 .
Gln Leu Lys Trp Lys Arg Pro Pro Asp Asn Glu Ala Leu Pro Val Pro 340 345 350
Phe Leu His Ala Gln Arg Tyr Val Ser Gly Tyr Gly Leu Gln Lys Gly 355 360 365
Glu Leu Ser Thr Leu Leu Tyr Asn Ser His Pro Tyr Arg Ala Phe Pro 370 380
Val Leu Leu Asp Ala Val Pro Trp Tyr Leu Arg Leu Tyr Val His 385 390 395 400
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Thr Leu Thr Ile Thr Ser Lys Gly Lys Asp Asn Lys Pro Ser Tyr Ile
             405
                                  410 415
His Tyr Gln Pro Ala Gln Asp Arg Gln Gln Pro His Leu Leu Glu Met 420 425 430
Leu Ile Gln Leu Pro Ala Asn Ser Val Thr Lys Val Ser Ile Gln Phe
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                           440
                                              445
Glu Arg Ala Leu Leu Lys Trp Thr Glu Tyr Thr Pro Asp Pro Asn His
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    450
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Gly Phe Tyr Val Ser Pro Ser Val Leu Ser Ala Leu Val Pro Ser Met 465 470 475 480
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Val Ala Ala Lys Pro Val Asp Trp Glu Glu Ser Pro Leu Phe Asn Thr
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Leu Phe Pro Val Ser Asp Gly Ser Ser Tyr Phe Val Arg Leu Tyr Thr
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                              505
Glu Pro Leu Leu Val Asn Leu Pro Thr Pro Asp Phe Ser Met Pro Tyr
515 520 525
Asn Val Ile Cys Leu Thr Cys Thr Val Val Ala Val Cys Tyr Gly Ser
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                                           540 .
   530
Phe Tyr Asn Leu Leu Thr Arg Thr Phe His Ile Glu Glu Pro Lys Ser
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Gly Gly Leu Ala Lys Arg Leu Ala Asn Leu Ile Arg Arg Ala Arg Gly
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              565
Val Pro Pro Leu
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      <211> 283
      <212> PRT
      <213> Rat
      <400> 308
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Asp Thr His Gln Trp Tyr Val Cys Asn Arg Glu Lys Leu Cys Glu Ser 20 25 30
           20
                                25
                                                   30
Leu Gln Ser Val Phe Val Gln Ser Tyr Leu Asp Gln Gly Thr Gln Ile
       35
                           40
Phe Leu Asn Asn Ser Ile Glu Lys Ser Gly Trp Leu Phe Ile Gln Leu
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60

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 Tyr
 His
 Ser
 Phe
 Val
 Ser
 Ser
 Val
 Phe
 Ser
 Leu
 Arg
 Fer
 Fer
 Fer
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 Ser
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Arg Ala Asp Val Leu

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Trp Ile Leu Phe Phe Val Leu Tyr Asp Phe Cys Ile Val Cys Ile Thr
      20
                              25
                                                  30
Thr Tyr Ala Ile Asn Val Ser Leu Met Trp Leu Ser Phe Arg Lys Val 35 40 45
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Gln Glu Pro Gln Gly Lys Ala Lys Arg His
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Leu Val Val Val Met Val Cys Tyr Phe Ile Leu Ser Ile Ile Asn Ser
                              25
Met Ala Gln Ser Tyr Ala Lys Arg Ile Gln Gln Arg Leu Asn Ser Glu
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Glu Lys Thr Lys
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Ala Asn Ser Arg Ser Ser Glu Asp Thr Lys Gln Met Met Ser Ser Phe
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Met Leu Ser Ile Ser Ala Val Val Met Ser Tyr Leu Gln Asn Pro Gln
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Pro Met Thr Pro Pro Trp
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Met Phe Ile Thr Pro Phe Lys Ala Phe Leu Pro Leu Tyr Leu Leu Thr
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Glu Leu Ser Leu Ile Asp Ile Thr Ser Cys Asp Asp Leu Pro His Ser 25 30 Val Leu Pro Gln His Leu Ser Phe Glu Phe Val Leu Trp Ser Met Tyr 35 40 45 Leu Leu Ile Cys Cys Phe Val Ile Ile Phe 50 55

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 Ser Leu Leu Leu Leu Ser Ser Val Phe Trp Phe Leu Val Arg Val Ile Thr

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 Asp Arg Asp Gly Pro Val Gln Asp Tyr Leu

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Ile Arg His Glu Ala Glu Ala Gly Arg His Gln Pro Glu Gln Leu Ala 10. Ala Asp Ser Arg Thr Glu Thr Val Gly Pro Arg Gln Ser Asn Gly Leu Thr Gly Pro Gly Leu Pro Thr Trp Gln Leu His Pro Val Leu Phe Pro 35 40 45 Glu Leu Val Leu Trp Val Asn Met Val Pro Cys Phe Leu Leu Ser Leu . 50 55 60 . Leu Leu Leu Val Arg Pro Ala Pro Val Val Ala Tyr Ser Val Ser Leu 65 70 75 80 75 Pro Ala Ser Phe Leu Glu Glu Val Ala Gly Ser Gly Glu Ala Glu Gly 85 90 95 Ser Pro Thr Pro Gly Arg Thr Gln Pro Thr Ala Pro Val Gly Pro Val 115 120 125 125 Pro Pro Thr Asn Leu Leu Asp Gly Ile Val Asp Phe Phe Arg Gln Tyr 130 135 140 Val Met Leu Ile Ala Val Val Gly Ser Leu Thr Phe Leu Ile Ser Ser

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155

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50 55 60 His His His His Leu Ala Ser Gly Ser His Lys Pro Leu Pro Leu 75 70 Leu Thr His Arg Phe Pro Phe Tyr Tyr Glu Phe Lys Met Ala Phe Val 85 90 95 Leu Trp Leu Leu Ser Pro Tyr Thr Lys Gly Ala Ser Leu Leu Tyr Arg Lys Phe Val His Pro Ser Leu Ser Arg His Glu Lys Glu Ile Asp Ala 115 120 125 Cys Ile Val Gln Ala Lys Glu Arg Ser Tyr Glu Thr Met Leu Ser Phe 130 135 140 Gly Lys Arg Ser Leu Asn Ile Ala Ala Ser Ala Ala Val Gln Ala Ala 145 150 150 155 160 150 160 Thr Lys Ser Gln Gly Ala Leu Ala Gly Arg Leu Arg Ser Phe Ser Met 165 170 175 Gln Asp Leu Arg Ser Ile Pro Asp Thr Pro Val Pro Thr Tyr Gln Asp 180 185 190 Pro Leu Tyr Leu Glu Asp Gln Val Pro Arg Arg Arg Pro Pro Ile Gly 195 200 205 Tyr Arg Pro Gly Gly Leu Gln Gly Ser Asp Thr Glu Asp Glu Cys Trp 215 220 210 Ser Asp Asn Glu Ile Val Pro Gln Pro Pro Val Gly Pro Arg Glu Lys 225 230 235 240 225 230 240
Pro Leu Gly Arg Ser Gln Ser Leu Arg Val Val Lys Arg Lys Pro Leu
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> <210> 324 <211> 166 <212> PRT <213> Rat

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Glu Ala Pro Val Cys Gly Val Thr Glu Glu Lys Pro Glu Val Pro Asp 275 280 Glu Thr Ala Ser Ala Glu Ala Glu Gly Val Pro Ala Ala Ser Glu Gly 290 295 300 . 300 Gln Gly Glu Pro Glu Gly Ser Phe Ser Leu Ala Gln Glu Pro Gln Gly 305 310 315 Ala Ala Gly Pro Ser Glu Arg Ser Cys Ala Cys Asn Arg Ile Ser Pro Asn Val

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Glu Glu Gly Gly Asn Ser Tyr Gly Glu Val Lys Val Lys Leu Ile Val 115 120 . 125 Leu Val Pro Pro Ser Lys Pro Thr Val Asn Ile Pro Ser Ser Ala Thr 130 135 140 Ile Gly Asn Arg Ala Val Leu Thr Cys Ser Glu Gln Asp Gly Ser Pro 155 Pro Ser Glu Tyr Thr Trp Phè Lys Asp Gly Ile Val Met Pro Thr Asn 165 170 175 Pro Lys Ser Thr Arg Ala Phe Ser Asn Ser Ser Tyr Val Leu Asn Pro 180 185 Thr Thr Gly Glu Leu Val Phe Asp Pro Leu Ser Ala Ser Asp Thr Gly 195 200 205 Glu Tyr Ser Cys Glu Ala Arg Asn Gly Tyr Gly Thr Pro Met Thr Ser 210 215 220 Asn Ala Val Arg Met Glu Ala Val Glu Arg Asn Val Gly Val Ile Val 230 235 Ala Ala Val Leu Val Thr Leu Ile Leu Leu Gly Ile Leu Val Phe Gly 245 250 255 Il'e Trp Phe Ala Tyr Ser Arg Gly His. Phe Asp Arg Thr Lys Lys Gly
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Cys Lys Pro Gly Phe Phe Gly Asp Gly Cys Leu Gln Gln Cys Asn Cys

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Leu 145	Lys	Pro	Ala	Asn	11e 150	Leu	Leu	qaA	Ala	His 155	Tyr	His	Val	Lys	11e 160
	Asp	Phe	Gly	Leu 165		Lys	Сув	Asn	Gly 170	Met	Ser	His	Ser	His 175	qaA
Leu	Ser	Met	Asp 180	Gly	Leu	Phe	Gly	Thr 185	Ile	Ala	Tyr	Leu	Pro 190	Pro	Glu
Arg	Ile	Arg 195		Lys	Ser	Arg	Leu 200	Phe	Asp	Thr	Lys	His 205	Asp	Val	Tyr <sub>.</sub>
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His	Arg	Pro	Glu	Leu 245	Pro	Pro	Ile	Cys	Arg 250	Pro	Arg	Pro	Arg	Ala 255	Сув
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	Arg	275					280					285	•		
	Lys 290					295					300				
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	Leu		340			_		345					350		
	Glu	355					360				_	365			
	Ser 370				•	375					380				
385	Ser	•	-		390					395					400
	Asp			405					410					415	
	Ile		420	_				425					430		
	Val	435					440					445			
	Glu 450		_			455					460				
465	Asn				470					475					480
	Val		_	485		_	_		490					495	
_	Thr		500			_	_	505			_		510		
	Ala	515					520					525			
_	530					535					540	_			
545	Val		-		550	_				555		_	•		560
_	Arg			565		_			570					575	
ьeu	His	тух	ALA	ATa	.r.tb	GTU	сŦĀ	nis	тел	PIO	тте	val	ьys	ьeu	neu

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725 730 735 Gln Gly Leu Ser Ala Leu His Leu Ala Ala Gln Gly Arg His Ser Gln 740 745 750 Thr Val Glu Thr Leu Leu Lys His Gly Ala His Ile Asn Leu Gln Ser 755 760 765 Leu Lys Phe Gln Gly Gly Gln Ser Ser Ala Ala Thr Leu Leu Arg Arg 775 770 780 Ser Lys Thr

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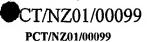
Ile Asp Leu Gly Asp Ser Cys Ile Thr Val Gly Asn Thr Thr His 20 25 30



Val Met Lys Asn Leu Leu Pro Glu Thr Thr Tyr Arg Ile Arg Ile Gln 40 35 Ala Ile Asn Glu Ile Gly Val Gly Pro Phe Ser Gln Phe Ile Lys Ala 55 50 60 Lys Thr Arg Pro Leu Pro Pro Ser Pro Pro Arg Leu Glu Cys Ala Ala 65 70 75 80 Ser Gly Pro Gln Ser Leu Lys Leu Lys Trp Gly Asp Ser Asn Ser Lys 85 90 95 Thr His Ala Ala Gly Asp Met Val Tyr Thr Leu Gln Leu Glu Asp Arg 100 105 110 100 Asn Lys Arg Phe Ile Ser Ile Tyr Arg Gly Pro Ser His Thr Tyr Lys 115 120 . 125 Val Gln Arg Leu Thr Glu Phe Thr Cys Tyr Ser Phe Arg Ile Gln Ala 130 135 140 Met Ser Glu Ala Gly Glu Gly Pro Tyr Ser Glu Thr Tyr Thr Phe Ser 145 150 155 160 145 155 Thr Thr Lys Ser Val Pro Pro Thr Leu Lys Ala Pro Arg Val Thr Gln
165 170 175 Leu Glu Gly Asn Ser Cys Glu Ile Phe Trp Glu Thr Val Pro Pro Met 180 185 Arg Gly Asp Pro Val Ser Tyr Val Leu Gln Val Leu Val Gly Arg Asp 195 200 205 Ser Glu Tyr Lys Gln Val Tyr Lys Gly Glu Glu Ala Thr Phe Gln Ile 210 215 220 Ser Gly Leu Gln Ser Asn Thr Asp Tyr Arg Phe Arg Val Cys Ala Cys 225 . 230 . 230 . 240 Arg Arg Cys Val Asp Thr Ser Gln Glu Leu Ser Gly Ala Phe Ser Pro 245 250 255 Ser Ala Ala Phe Met Leu Gln Gln Arg Glu Val Met Leu Thr Gly Asp 260 265 270 265 260 270 Leu Gly Gly Met Glu Glu Ala Lys Met Lys Gly Met Met Pro Thr Asp 275 280 285 Glu Gln Phe Ala Ala Leu Ile Val Leu Gly Phe Ala Thr Leu Ser Ile 290 295 300 Leu Phe Ala Phe Ile Leu Gln Tyr Phe Leu Met Lys 310

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Gln Thr Asn Trp Thr Val Pro Thr Ser Glu Asp Val Thr Lys Val Asn 120 125 Leu Gln Val Leu Ile Val Val Asn Arg Thr Ala Ser Lys Ser Ser Val 135 130 140 Lys Met Glu Gln Val Gln Pro Ser Ala Ser Thr Pro Ile Pro Glu Ser 145 150 155 Ser Glu Thr Ser Gln Thr Ile Asn Thr Thr Pro Thr Val Asn Thr Ala 165 170 175 Lys Thr Thr Ala Lys Asp Thr Ala Asn Thr Thr Ala Val Thr Thr Ala 180 185 190 Asn Thr Thr Ala Asn Thr Thr Ala Val Thr Thr Ala Lys Thr Thr Ala 195 200 205 Lys Ser Leu Ala Ile Arg Thr Leu Gly Ser Pro Leu Ala Gly Ala Leu 210 215 220 His Ile Leu Leu Val Phe Leu Ile Ser Lys Leu Leu Phe 230 235

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<213> Mouse

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265

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Ser Asp Gln Glu Thr Leu Arg Ile His Glu Arg Leu Val Ala Gly Ser Leu Ala Gly Ala Ile Ala Gln Ser Ser Ile Tyr Pro Met Glu Val Leu Lys Thr Arg Met Ala Leu Arg Lys Thr Gly Gln Tyr Ser Gly Met Leu Asp Cys Ala Arg Arg Ile Leu Ala Lys Glu Gly Val Ala Ala Phe Tyr Lys Gly Tyr Ile Pro Asn Met Leu Gly Ile Ile Pro Tyr Ala Gly Ile Asp Leu Ala Val Tyr Glu Thr Leu Lys Asn Thr Trp Leu Gln Arg Tyr Ala Val Asn Ser Ala Asp Pro Gly Val Phe Val Leu Leu Ala Cys Gly Thr Ile Ser Ser Thr Cys Gly Gln Leu Ala Ser Tyr Pro Leu Ala Leu Val Arg Thr Arg Met Gln Ala Gln Ala Ser Ile Glu Gly Ala Pro Glu Val Thr Met Ser Ser Leu Phe Lys Gln Ile Leu Arg Thr Glu Gly Ala Phe Gly Leu Tyr Arg Gly Leu Ala Pro Asn Phe Met Lys Val Ile Pro Ala Val Ser Ile Şer Tyr Val Val Tyr Glu Asn Leu Lys Ile Thr Leu Gly Val Gln Ser Arg 

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<213> Mouse

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<210> 341 <211> 431 <212> PRT <213> Mouse

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California   Cal					20					0.5					70		
S	G3	<b>.</b>	T.011	arr.	20	Dho	7~~	Dha	T.OU	25	y cz.	1721	7.1.	C111	30 Tur	a۲۵	Car.
Tyr Leu Glu Thr Gly Arg Gly Leu   Cys Phe   Pro Leu Val Lys   Ala   Cys   Cys   Phe   Pro Leu Val Lys   Ala   Cys   Cys   Cys   Ala   Pro   Ala   Pro   Ala   Pro   Pro   Val Lys   Ala   Pro   Pro   Pro   Val Lys   Ala   Pro				35					40					45			
Val   Phe   Gly   Ash   Glu   Pro   Lys   Ala   Pro   Ash   Glu   Val   Leu   Leu   Ala   Pro   Pro   Pro   Ash   Glu   Val   Leu   Leu   Ala   Pro		50		•	_	_	55				_	60					
S			Leu	Glu	Thr	Gly		Gly	Leu	Сув	Phe		Leu	Val	Lys	Ala	
Val   Phe   Cys   Ala   Ser   Cly   Leu   Cln   Val   Ser   Tyr   Leu   Thr   Trp   Cly   Ile   115   125   125   125   125   126   125   126   125   126   125   126	۷a	1	Phe	Gly	Asn		Pro	Lys	Ala	Pro	_	Glu	Val	Leu	Leu		Pro
Name	Ar	g	Thr	Ģlu		Ala	Glu	Ser	Thr		Ser	Trp	Gln	Val		Lys	Leu
Leu   Gln   Glu   Arg   Val   Met   Thr   Gly   Ser   Tyr   Gly   Ala   Thr   Ala   Thr   Ser   Ser   Gly   Glu   His   Phe   Thr   Asp   Ser   Gln   Phe   Leu   Val   Leu   Met   Asp   Asp   Asp   Ser   Gln   Phe   Leu   Val   Leu   Met   Asp   Asp   Asp   Ser   Gln   Tyr   Cys   Val   Leu   Met   Asp   Asp   Gln   Asp   Tyr   Cys   Val   Leu   Arg   Lys   Gln   Tyr   Cys   Tyr   Cys   Val   Leu   Arg   Lys   Gln   Tyr   Cys   Tyr   Cys   Tyr   Cys   Cys   Tyr   Cys    Va	1	Phe	-	Ala	Ser	Gly	Leu		Val	Ser	Tyr	Leu		Trp	Gly	Ile	
Pro Gly Glu His Phe Thr Asp Ser Gln Phe Leu Val Leu Met Asn Arg 145	Le				Arg	Val	Met			Ser	Tyr	Gly			Ala	Thr	Ser
145	Pr			Glu	His	Phe	Thr		Ser	Gln	Phe	Leu		Leu	Met	Asn	Ara
The late   Fig.   Fig			•														_
Asn Val Leu Ser Ser Try Cys Gln Tyr Glu Ala Leu Lys Phe Val Ser 195	Va	1 :	Leu	Ala	Leu •		Val	Ala	Gly	Leu		Суз	Val	Leu	Arg		Gln
Pro   Thr   Gln   Val   Leu   Ala   Lys   Ala   Ser   Lys   Val   Tile   Pro   Val   Met	Pr	ο.	Arg	His	_	Ala	Pro	Met	Tyr	_	Tyr	Ser	Phe	Ala		Leu	Ser
Met Met Gly Lys Leu Val Ser Arg Arg Ser Tyr Glu His Trp Glu Tyr 225   230   230   235   240	As	n	Val		Ser	Ser	Trp	Сув		Tyr	Glu	Ala	Leu		Phe	Val	Ser
Met         Met         Gly         Lys         Leu         Val         Ser         Arg         Arg         Ser         Tyr         Glu         His         Trp         Glu         Tyr         240           Leu         Thr         Ala         Gly         Leu         Ile         Gly         Val         Ser         Met         Phe         Leu         Leu         Ser         250         Leu         255         255         255         255         255         255         255         255         255         255         255         255         255         255         250         270         280         270         280         270         280         270         280         270         280         270         280         270         280         270         280         270         280         270         280         270         280	Ph			Thr	Gln	Val	Leu		Lув	Ala	Ser	Lys		Ile	Pro	Val	Met
Leu Thr         Ala Gly         Leu Ile         Ser         Ile         Gly         Val         Ser         Met         Phe         Leu         Leu         Ser         255         Ser         250         Cor         255         Ser         Gly         Leu         Ser         Gly         Leu         255         Ser         Phe         Thr         Leu         255         Cly         Leu         265         270         280         270         280         270         280         270         285         Cly         Leu         Phe         Asp         Ser         Asp		t :		Gly	Lys	Leu			Arg	Arg	Ser			His	Trp	Glu	_
Ser Gly         Pro Glu         Pro Arg         Ser Ser         Pro Ala         Thr         Leu         Ser Gly         Leu           Val         Leu         Leu         Ala         Gly         Tyr         Ile         Ala         Phe         Asp         Ser         Phe         Thr         Ser         Asp         Phe         Thr         Ser         Asp         Thr         Asp         Asp         Thr         Asp         Thr         Asp         Asp         Thr         Asp         Thr         Asp         Asp         Thr         Asp         Thr         Asp         Thr         Asp         Thr         Asp         Asp         Thr         Asp         Thr         Asp         Asp         Thr         Asp         Thr         Asp         Thr         Asp         Thr         Asp         Thr         Asp         Asp         Thr         Asp         Thr         Asp         Thr         Asp         Asp         Thr         Asp         Thr         Asp <td></td> <td></td> <td>Thr</td> <td>Ala</td> <td>Gly</td> <td></td> <td></td> <td>Ser</td> <td>Ile</td> <td>Gly</td> <td></td> <td></td> <td>Met</td> <td>Phe</td> <td>Leu</td> <td></td> <td></td>			Thr	Ala	Gly			Ser	Ile	Gly			Met	Phe	Leu		
Val         Leu         Leu         Ala         Gly         Tyr         Ile         Ala         Phe         Asp         Ser         Phe         Thr         Ser         Asp         Thr         Ser         Asp         Thr         Ser         Asp         Image: Assistance of the context of t	Se	r	Gly	Pro			Arg	Ser	Ser			Thr	Thr	Leu			Leu
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Gly Val Asn Leu Phe Ser Cys Leu Phe Thr Val Gly Ser Leu Leu Glu 305	G1		_		Ŀeu	Phe	Ala	_		Met	Ser	Ser			Met	Met	Phe
305	G1			Asn	Leu	Phe	Ser		Leu	Phe	Thr	Val		Ser	Leu	Leu	Glu
Second Second			•					_					-				
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370 Leu Tyr Gly His Thr Val Thr Val Val Gly Gly Leu Gly Val Ala Val 385 390 Val Phe Thr Ala Leu Leu Leu Arg Val Tyr Ala Arg Gly Arg Lys Gln 405 Arg Gly Lys Lys Ala Val Pro Thr Glu Pro Pro Val Gln Lys Val	Le	u :	Phe		Phe	Тут	Thr	Ile		Gln	Phe	Gly	Ala		Va1	Phẹ	Thr
Leu Tyr Gly His Thr Val Thr Val Val Gly Gly Leu Gly Val Ala Val 385 390 395 . 400  Val Phe Thr Ala Leu Leu Leu Arg Val Tyr Ala Arg Gly Arg Lys Gln 405  Arg Gly Lys Lys Ala Val Pro Thr Glu Pro Pro Val Gln Lys Val	Il		_	Met	Thr	Leu	Arg			Ile	Ala	Ile			Ser	Cys	Leu
Val Phe Thr Ala Leu Leu Leu Arg Val Tyr Ala Arg Gly Arg Lys Gln 405 410 415 Arg Gly Lys Lys Ala Val Pro Thr Glu Pro Pro Val Gln Lys Val			Tyr	Gly	His	Thr			Val	Val	Gly			Gly	Val	Ala	
Arg Gly Lys Lys Ala Val Pro Thr Glu Pro Pro Val Gln Lys Val			Phe	Thr	Ala			Leu	Arg	Val			Arg	Gly	Arg		
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PCT/NZ01/00099

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 Pro
 Lys
 Tyr
 Pro
 His
 Cys
 Glu
 Glu
 Lys

 Met
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 Ile
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WO 01/90357

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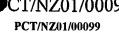
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aaa						5583

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<400> 373

 Met
 Pro
 Leu
 Pro
 Leu
 Leu
 Leu
 Ala
 Ala
 Leu
 Cys
 Leu
 Ala
 Ala
 Ser
 Pro

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50 55 60

Gln Tyr Gln Ala Gly Glu Gly Gly Leu Phe Tyr Ser Ala Glu Val Glu
65 70 75 80

Met Leu Val
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<210> 374 <211> 405 <212> PRT

<213> Mouse

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```
360
Val Glm Ala Val Leu Arg Glu Asp Ser Arg Ala Arg Val Gly Ile Ala
    370
                      375
                                           380
Ser Tyr Gly Arg Asn Leu Met Val Ala Val Pro Cys Arg Gly Val Pro
385 390
                                        395
Ala Leu Cys Arg Thr
                405
      <210> 375
      <211> 180
      <212> PRT
      <213> Mouse
      <400> 375
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                                    10
Met Val Val Ala Gly Val Val Ala Leu Thr Leu Ala Leu Val Leu Ala
          20
                               25
                                                    30
Trp Leu Ser Thr Tyr Val Ala Asp Ser Gly Asn Asn Gln Leu Leu Gly
       35
                           40
Thr Ile Val Ser Ala Gly Asp Thr Ser Val Leu His Leu Gly His Val 50 55 60
                                          60
Asp Gln Leu Val Asn Gln Gly Thr Pro Glu Pro Thr Glu His Pro His 65 70 75 80
Pro Ser Gly Gly Asn Asp Asp Lys Ala Glu Glu Thr Ser Asp Ser Gly
             85
                               90
Gly Asp Ala Thr Gly Glu Pro Gly Ala Arg Gly Glu Met Glu Pro Ser
100 105 110
Leu Glu His Leu Leu Asp Ile Gln Gly Leu Pro Lys Arg Gln Ala Gly 115 · 120 125
Leu Gly Ser Ser Arg Pro Glu Ala Pro Leu Gly Leu Asp Asp Gly Ser
130 135 140
130 135 140 Cys Leu Ser Pro Ser Pro Ser Leu Ile Asn Val Arg Leu Lys Phe Leu 145 150 150 160
Asn Asp Thr Glu Glu Leu Ala Val Ala Arg Pro Glu Asp Thr Val Gly
      165
                                    170
Thr Leu Lys Arg
           180
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      <211> 68
      <212> PRT
      <213> Mouse
      <400> 376
Met Cys Leu Pro Val Thr Val Trp Cys His Trp Ala Leu Trp Val Ala 1 10 .. 15
His Leu Pro Leu Ile Pro Ser Val Gly Lys Ser Gln Cys Thr Gln Met 20 25 30
Trp His Cys Cys Met Pro Trp Val Cys Val Gly Asp Cys Leu Cys Leu
   . 35
                           40
Ser Asp Pro Leu Trp Leu Cys Leu Leu Lys Glu Thr Glu Thr Pro Cys
Gly Phe Leu Ser
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<210> 377

<211> 107 <212> PRT <213> Rat

105

<210> 378 <211> 95 <212> PRT <213> Rat

100

| Secondary Seco

65 70 75 Ala His Thr Ser Met Asp Arg Thr Leu Gly Leu Leu Ser Cys Cys 85 90 95

<210> 379 <211> 138 <212> PRT <213> Mouse

| Met | Asp | Leu | Asp | Val | Val | Asn | Met | Phe | Val | Ile | Ala | Gly | Gly | Thr | Leu | Leu | Ile | Pro | Ser | 25 | Ser | Phe | Leu | Leu | Trp | Pro | Ser | Ser | Ser | Ser | Ser | Pro | Leu | Trp | Pro | Ser | Ser | Ser | Ser | Ser | Pro | Leu | Trp | Pro | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser | Ser |

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Asn Leu His Leu Val Cys Val Asp Met Pro Gly His Glu Gly Thr Thr 100 105 110.
                                                       110.
Arg Ser Ser Leu Asp Asp Leu Ser Ile Val Gly Gln Val Lys Arg Ile
115 120 125
His Gln Phe Val Glu Cys Leu Lys Leu Asn
                         135
      <210> 380
      <211> 81
      <212> PRT
      <213> Rat
      <400> 380
Met Ala Ser Ser Ser Asn Trp Leu Ser Gly Val Asn Val Val Leu Val
                                      10
Met Ala Tyr Gly Ser Leu Val Phe Val Leu Leu Phe Ile Phe Val Lys
20 25 30
Arg Gln Ile Met Arg Phe Ala Met Lys Ser Arg Arg Gly Pro His Val
35 40 45
Pro Val Gly His Asn Ala Pro Lys Asp Leu Lys Glu Glu Ile Asp Ile 50 55 60
Arg Leu Ser Arg Val Gln Asp Ile Lys Tyr Glu Pro Gln Leu Leu Ala
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<210> 381 <211> 257 <212> PRT <213> Mouse 70

65

Asp

<400> 381

Met Arg Ser Gly Ala Leu Trp Pro Leu Leu Trp Gly Ala Leu Val Trp

1 10 15 10 Thr Val Gly Ser Val Gly Ala Val Met Gly Ser Glu Asp Ser Val Pro 20 25 30 25 30 Gly Gly Val Cys Trp Leu Gln Gln Gly Arg Glu Ala Thr Cys Ser Leu . 35 40 45 Val Leu Lys Thr Arg Val Ser Arg Glu Glu Cys Cys Ala Ser Gly Asn 50 55 60 Ile Asn Thr Ala Trp Ser Asn Phe Thr His Pro Gly Asn Lys Ile Ser 65 70 75 80 Leu Leu Gly Phe Leu Gly Leu Val His Cys Leu Pro Cys Lys Asp Ser • .85 90 95 90 .85 Cys Asp Gly Val Glu Cys Gly Pro Gly Lys Ala Cys Arg Met Leu Gly 100 105 110 Gly Arg Pro Thr Leu Arg Ser Cys Val Pro Asn Cys Glu Gly Leu Pro 115 120 125 Ala Gly Phe Gln Val Cys Gly Ser Asp Gly Ala Thr Tyr Arg Asp Glu 130 135 140 Cys Glu Leu Arg Thr Ala Arg Cys Arg Gly His Pro Asp Leu Arg Val 145 150 155 160 Met Tyr Arg Gly Arg Cys Gln Lys Ser Cys Ala Gln Val Val Cys Pro 165 170 175 Arg Pro Gln Ser Cys Leu Val Asp Gln Thr Gly Ser Ala His Cys Val 180 190 185 Val Cys Arg Ala Ala Pro Cys Pro Val Pro Ser Asn Pro Gly Gln Glu

200

205

195

```
Leu Cys Gly Asn Asn Asn Val Thr Tyr Ile Ser Ser Cys His Leu Arg
210 215 220
Gln Ala Thr Cys Phe Leu Gly Arg Ser Ile Gly Val Arg His Pro Gly
225
               230
                                           235 ·
Ile Cys Thr Gly Gly Pro Lys Val Pro Ala Glu Glu Glu Asn Phe
                245
                                        250
Val
       <210> 382
       <211> 285
       <212> PRT
       <213> Rat
       <400> 382
Met Ile Ser Trp Met Leu Leu Ala Cys Ala Leu Pro Cys Ala Ala Asp

1 5 10 15
Pro Met Leu Gly Ala Phe Ala Arg Arg Asp Phe Gln Lys Gly Gly Pro 20 25 30
Gln Leu Val Cys Ser Leu Pro Gly Pro Gln Gly Pro Pro Gly Pro Pro 35 40 45
Gly Ala Pro Gly Ser Ser Gly Met Val Gly Arg Met Gly Phe Pro Gly 50 55 60
Lys Asp Gly Gln Asp Gly Gln Asp Gly Asp Arg Gly Asp Ser Gly Glu 65 70 75 80
Glu Gly Pro Pro Gly Arg Thr Gly Asn Arg Gly Lys Gln Gly Pro Lys
85 90 95
Gly Lys Ala Gly Ala Ile Gly Arg Ala Gly Pro Arg Gly Pro Lys Gly
100 105 110
Val Ser Gly Thr Pro Gly Lys His Gly Ile Pro Gly Lys Lys Gly Pro
115 120 125
Lys Gly Lys Lys Gly Glu Pro Gly Leu Pro Gly Pro Cys Ser Cys Gly 130 135 140
Ser Ser Arg Ala Lys Ser Ala Phe Ser Val Ser Val Thr Lys Ser Tyr
145 150 155 160
Pro Arg Glu Arg Leu Pro Ile Lys Phe Asp Lys Ile Leu Met Asn Glu
165 170 175
Gly Gly His Tyr Asn Ala Ser Ser Gly Lys Phe Val Cys Ser Val Pro
180 185 190
Gly Ile Tyr Tyr Phe Thr Tyr Asp Ile Thr Leu Ala Asn Lys His Leu
195 200 205
Ala Ile Gly Leu Val His Asn Gly Gln Tyr Arg Ile Arg Thr Phe Asp 210 215 220
Ala Asn Thr Gly Asn His Asp Val Ala Ser Gly Ser Thr Ile Leu Ala
225 230 235 240
Leu Lys Glu Gly Asp Glu Val. Trp Leu Gln Ile Phe Tyr Ser Glu Gln 245 250 255
Asn Gly Leu Phe Tyr Asp Pro Tyr Trp Thr Asp Ser Leu Phe Thr Gly 260 265 270
                                  265
Phe Leu Ile Tyr Ala Asp Gln Gly Asp Pro Asn Glu Val
        275
                               280
      <210> 383
      <211> 183
      <212> PRT
      <213> Rat
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<400> 383 Met Lys Leu Cys Leu Val Ala Val Val Gly Cys Leu Leu Val Pro 1 5 10 Pro Ala Gln Ala Asn Lys Ser Ser Glu Asp Ile Arg Cys Lys Cys Ile 20 25 30 Cys Pro Pro Tyr Arg Asn Ile Ser Gly His Ile Tyr Asn Gln Asn Val 45 Ser Gln Lys Asp Cys Asn Cys Leu His Val Val Glu Pro Met Pro Val 50 60 Pro Gly His Asp Val Glu Ala Tyr Cys Leu Leu Cys Glu Cys Arg Tyr 65 70 75 80 Glu Glu Arg Ser Thr Thr Thr Ile Lys Val Ile Ile Val Ile Tyr Leu 85 90 95 Ser Val Val Gly Ala Leu Leu Leu Tyr Met Ala Phe Leu Met Leu Val Asp Pro Leu Ile Arg Lys Pro Asp Ala Tyr Thr Glu Gln Leu His Asn 115 120 125 Glu Glu Glu Asn Glu Asp Ala Arg Ser Met Ala Ala Ala Ala Ala Ser 130 135 140 140 Ile Gly Gly Pro Arg Ala Asn Thr Val Leu Glu Arg Val Glu Gly Ala 145 150 155 160 Gln Gln Arg Trp Lys Leu Gln Val Gln Glu Gln Arg Lys Thr Val Phe 165 170 175 170 Asp Arg His Lys Met Leu Ser 180

<210> 384 <211> 292 <212> PRT

<213> Mouse

<400> 384 Cys Gln Leu Pro Leu Arg Val Leu Ile Ile Ser Asn Asn Lys Leu Gly 10 Ala Leu Pro Pro Asp Ile Ser Thr Leu Gly Ser Leu Arg Gln Leu Asp 20 25 30 Val Ser Ser Asn Glu Leu Gln Ser Leu Pro Val Glu Leu Cys Ser Leu 35 40 45 45 Arg Ser Leu Arg Asp Leu Asn Val Arg Arg Asn Gln Leu Ser Thr Leu 50 60 55 60 Pro Asp Glu Leu Gly Asp Leu Pro Leu Val Arg Leu Asp Phe Ser Cys 65 70 75 80 Asn Arg Ile Ser Arg Ile Pro Val Ser Phe Cys Arg Leu Arg His Leu 85 90 95 Gln Val Val Leu Leu Asp Ser Asn Pro Leu Gln Ser Pro Pro Ala Gln 100 105 . 110 Ile Cys Leu Lys Gly Lys Leu His Ile Phe Lys Tyr Leu Thr Met Glu 115 120 125 Ala Gly Arg Arg Gly Ala Ala Leu Gly Asp Leu Val Pro Ser Arg Pro 130 135 140 140 Pro Ser Phe Ser Pro Cys Pro Ala Glu Asp Leu Phe Pro Gly Arg Arg 145 150 155 160 155 . Tyr Asp Gly Gly Leu Asp Ser Gly Phe His Ser Val Asp Ser Gly Ser 165 170 175 Lys Arg Trp Ser Gly Asn Glu Ser Thr Asp Asp Phe Ser Glu Leu Ser 185 190

<210> 385 <211> 164 <212> PRT

<213> Mouse

Ser Arg Gln Leu Arg Ala Pro Arg Phe Asp Pro Arg Ala Gly Phe His 1 5 10 15 Ala Glu Gly Lys Asp Arg Gly Pro Ser Val Pro Gln Gly Leu Leu Lys 20 25 30 Ala Ala Arg Ser Ser Gly Gln Leu Asn Leu Ala Gly Arg Asn Leu Gly 35 40 45 Glu Val Pro Gln Cys Val Trp Arg Ile Asn Val Asp Ile Pro Glu Glu
50 55 60 Ala Asn Gln Asn Leu Ser Phe Ser Ser Thr Glu Arg Trp Trp Asp Gln 65 70 75 80 75 Thr Asp Leu Thr Lys Leu Ile Ile Ser Ser Asn Lys Leu Gln Ser Leu 85 90 95 Ser Asp Asp Leu Arg Leu Leu Pro Ala Leu Thr Val Leu Asp Ile His 100 105 110 Asp Asn Gln Leu Thr Ser Leu Pro Ser Ala Ile Arg Glu Leu Asp Asn 115 120 125 Leu Gln Lys Leu Asn Val Ser His Asn Lys Leu Lys Ile Leu Pro Glu 130 . 135 140 Glu Ile Thr Ser Leu Lys Asn Leu Arg Thr Leu His Leu Gln His Asn 150 155 160 Glu Leu Thr Cys

<210> 386 <211> 71' <212> PRT <213> Mouse

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Val Gln Ser Ser Phe Leu Gly

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<210> 387
      <211> 126
      <212> PRT
      <213> Mouse
      <400> 387
Glu Tyr Glu Ala Arg Val Leu Glu Lys Ser Leu Arg Lys Glu Ser Arg
                                  10
Asn Lys Glu Thr Asp Lys Val Lys Leu Thr Trp Arg Asp Arg Phe Pro
           20
                              25
                                                  30
Ala Tyr Phe Thr Asn Leu Val Ser Ile Ile Phe Met Ile Ala Val Thr
35 40 45
                                             45
Phe Ala Ile Val Leu Gly Val Ile Ile Tyr Arg Ile Ser Thr Ala Ala
  50
                     55
                                        60
Ala Leu Ala Met Asn Ser Ser Pro Ser Val Arg Ser Asn Ile Arg Val
    70
                                     75
Thr Val Thr Ala Thr Ala Val Ile Ile Asn Leu Val Val Ile Ile Leu
                                 90
              85
Leu Asp Glu Val Tyr Gly Cys Ile Ala Arg Trp Leu Thr Lys Ile Gly 100 105 110
Glu Cys His Val Gln Asp Ser Ile Gly Ser Met Gly Leu Gly
                         120
       115
      <210> 388
<211> 84
      <212> PRT
      <213> Rat
    <400> 388
Ala Ala Glu Asn Glu Met Pro Val Ala Val Gly Pro Tyr Gly Gln Ser
               5
                                 10
Gln Pro Ser Cys Phe Asp Arg Val Lys Met Gly Phe Val Met Gly Cys 20 25 30
Ala Val Gly Met Ala Ala Gly Ala Leu Phe Gly Thr Phe Ser Cys Leu 35 40 45
Arg Ile Gly Met Arg Gly Arg Glu Leu Met Gly Gly Ile Gly Lys Thr
                      55
   50
                                         60
Met Met Gln Ser Gly Gly Thr Phe Gly Thr Phe Met Ala Ile Gly Met
                   70
Gly Ile Arg Cys
     <210> 389
     <211> 284
      <212> PRT
      <213> Rat
     <400> 389
Gly Gly Ser Ser Val Ser His Val Leu Arg Gly Ser Gly Gln Glu Arg
               5
                                10
                                                     15
Ser Pro Pro Pro Ala Ser Met Gln Pro Pro Trp Gly Leu Ala Leu Pro
          20
                             25
Leu Leu Pro Trp Val Ala Gly Gly Val Gly Thr Ser Pro Arg Asp
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Tyr Trp Leu Pro Ala Leu Ala His Gln Pro Gly Val Cys His Tyr Gly 50 55 60
Thr Lys Thr Ala Cys Cys Tyr Gly Trp Lys Arg Asn Ser Lys Gly Val 65 70 75 80
Cys Glu Ala Val Cys Glu Pro Arg Cys Lys Phe Gly Glu Cys Val Gly
85 90 95
Pro Asn Lys Cys Arg Cys Phè Pro Gly Tyr Thr Gly Lys Thr Cys Ser
100 105 110
Gln Asp Val Asn Glu Cys Ala Phe Lys Pro Arg Pro Cys Gln His Arg
115 120 125
Cys Val Asn Thr His Gly Ser Tyr Lys Cys Phe Cys Leu Ser Gly His
130 135 140
Met Leu Leu Pro Asp Ala Thr Cys Ser Asn Ser Arg Thr Cys Ala Arg
145 150 155 160
Ile Asn Cys Gln Tyr Ser Cys Glu Asp Thr Ala Glu Gly Pro Arg Cys 165 170 175
Val Cys Pro Ser Ser Gly Leu Arg Leu Gly Pro Asn Gly Arg Val Cys
180 185 190
Leu Asp Ile Asp Glu Cys Ala Ser Ser Lys Ala Val Cys Pro Ser Asn 195 200 205
       195
Arg Arg Cys Val Asn Thr Phe Gly Ser Tyr Tyr Cys Lys Cys His Ile
210 215 220
Gly Phe Glu Leu Lys Tyr Ile Ser Arg Arg Tyr Asp Cys Val Asp Ile
225 230 235 240
Asn Glu Cys Thr Leu Asn Thr Arg Thr Cys Ser Pro His Ala Asn Cys
245 250 255
Leu Asn Thr Gln Gly Ser Phe Lys Cys Lys Cys Lys Gln Gly Tyr Arg
260 265 270
Gly Asn Gly Leu Gln Cys Ser Val Ile Pro Glu His
        275
                               280
       <210> 390
       <211> 85
       <212> PRT
       <213> Rat
       <400> 390
Gly Ala Pro Met Tyr Phe Ser Glu Gly Arg Glu Arg Gly Lys Val Tyr
1 5 10 15
Val Tyr Asn Leu Arg Gln Asn Arg Phe Val Phe Asn Gly Thr Leu Lys 20 25 30
Asp Ser His Ser Tyr Gln Asn Ala Arg Phe Gly Ser Cys Ile Ala Ser 35 40 45
Val Gln Asp Leu Asn Gln Asp Ser Tyr Asn Asp Val Val Gly Ala 50 55 60 .
Pro Gln Glu Asp Ser His Arg Gly Ala Ile Tyr Ile Phe His Gly Phe 65 70 75 80
Gln Thr Asn Ile Leu
      <210> 391
       <211> 158
       <212> PRT
       <213> Rat
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<400> 391

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> Phe Gln Thr Asn Ile Leu Lys Lys Pro Val Gln Arg Ile Ser Ala Ser Glu Leu Ala Pro Gly Leu Gln His Phe Gly Cys Ser Ile His Gly Gln Leu Asp Leu Asn Glu Asp Gly Leu Val Asp Leu Ala Val Gly Ala Leu 35 40 45 Gly Asn Ala Val Val Leu Trp Ala Arg Pro Val Val Gln Île Asn Ala 50 55 60 60 Ser Leu His Phe Glu Pro Ser Lys Ile Asn Ile Phe His Lys Asp Cys 70 75 Lys Arg Asn Gly Arg Asp Ala Thr Cys Leu Ala Ala Phe Leu Cys Phe 85 90 95 Gly Pro Ile Phe Leu Ala Pro His Phe His Thr Ala Thr Val Gly Ile 100 105 110 Arg Tyr Asn Ala Thr Met Asp Glu Arg Arg Tyr Met Pro Arg Ala His 115 120 125 Leu Asp Glu Gly Ala Asp Gln Phe Thr Asn Arg Ala Val Leu Leu Ser 130 135 140 Ser Gly Gln Glu His Cys Gln Arg Ile Asn Phe His Val Leu 150

<210> 392

<211> 124

<212> PRT

<213> Mouse

<400> 392

Ala Ala Glu Gln Glu Ala Ser Ser Arg Arg Arg Arg Gly Gly Ala Gly
1 5 10 15 Pro Ala Leu Phe Ser Ser Gly Ser Leu Arg Ser Glu Pro Gln Pro Arg 20 25 30 Leu Pro Gln Ala Arg Ser Arg Pro Arg Pro Ser Phe Leu Gln Ala Arg 35 40 45 Ser Arg Pro Cys Leu Ser Gln Ala Cys Ser Pro Ala Ala Ser Val Leu 50 55 60 Ser Ser Ser Leu Cys Gly Arg Ser His Leu Leu Pro Gly Ser Leu 65 70 75 80 Pro Ala Thr Ala Phe Leu Leu Leu Pro Gly Ser Leu Pro Gly Arg 85 90 Arg Pro Ser Ala Ala Gln Ala Ala Pro Val Leu Ala Trp Gly Leu Val 100 105 Ala Phe Gln Leu Gly Val Ala Ala Gly Ala Gly Arg 115 120

<210> 393

<211> 242

<212> PRT

<213> Rat

<400> 393

Gly His Cys Asp Cys Gln Ala Gly Tyr Gly Glu Glu Ala Cys Gly Gln 1 5 10 15 Cys Gly Leu Gly Tyr Phe Glu Ala Glu Arg Asn Ser Ser His Leu Val 20 25 30 Cys Ser Ala Cys Phe Gly Pro Cys Ala Arg Cys Thr Gly Pro Glu Glu 35 40 45 Ser His Cys Leu Gln Cys Arg Lys Gly Trp Ala Leu His His Leu Lys

<210> 394 <211> 99 <212> PRT <213> Mouse

 400>
 394

 Met
 Arg
 Leu
 Ala
 Ala
 Leu
 <210> 395 <211> 103 <212> PRT <213> Human

<210> 396 <211> 1529 <212> PRT <213> Rat

 <400>
 396

 Met
 Ser
 Gly
 Ile
 Gly
 Trp
 Gln
 Thr
 Leu
 Ser
 Leu
 Ala
 Leu
 Ala
 Cys
 Leu
 Ala
 Leu
 Ala
 Cys
 Pro
 Ala
 Gln
 Cys

 Leu
 Asr
 Ile
 Leu
 Asr
 Asr
 Cys
 His
 Gly
 Leu
 Ala
 Gly
 Leu
 Arg
 Ser

 Ser
 Cys
 Ser
 Gly
 Ser
 Thr
 Val
 Asp
 Cys
 His
 Gly
 Leu
 Ala
 Leu
 Arg
 Ser

 Val
 Pro
 Arg
 Asr
 Ile
 Thr
 Lys
 Thr
 Asr
 Phe
 Ala
 Gly
 Leu
 Arg
 <td

Ala Ser Phe Asn Ris Met Pro Lys Leu Arg Thr Phe Arg Leu His Ser
195 200 205

Asn Asn Leu Tyr Cys Asp Cys His Leu Ala Trp Leu Ser Asp Trp Leu
210 215 220

Arg Gln Arg Pro Arg Val Gly Leu Tyr Thr Gln Cys Met Gly Pro Ser 225 230 235 240

His Leu Arg Gly His Asn Val Ala Glu Val Gln Lys Arg Glu Phe Val 245 250 255

Cys Ser Gly His Gln Ser Phe Met Ala Pro Ser Cys Ser Val Leu His 260 270 265 270

Cys Pro Ile Ala Cys Thr Cys Ser Asn Asn Ile Val Asp Cys Arg Gly 275 280 280 285

Lys Gly Leu Thr Glu Ile Pro Thr Asn Leu Pro Glu Thr Ile Thr Glu
290 295 300

Ile Arg Leu Glu Gln Asn Ser Ile Arg Val Ile Pro Pro Gly Ala Phe
305 310 315 320

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Ser Pro Tyr Lys Lys Leu Arg Arg Leu Asp Leu Ser Asn Asn Gln Ile
325 330 335
Ser Glu Leu Ala Pro Asp Ala Phe Gln Gly Leu Arg Ser Leu Asn Ser 340 345 350
Leu Val Leu Tyr Gly Asn Lys Ile Thr Glu Leu Pro Lys Ser Leu Phe
355 360 365
Glu Gly Leu Phe Ser Leu Gln Leu Leu Leu Leu Asn Ala Asn Lys Ile
    370
                375
                                        380
Asn Cys Leu Arg Val Asp Ala Phe Gln Asp Leu His Asn Leu Asn Leu
385 390 395 400
Leu Ser Leu Tyr Asp Asn Lys Leu Gln Thr Val Ala Lys Gly Thr Phe
405 410 415
Ser Ala Leu Arg Ala Ile Gln Thr Met His Leu Ala Gln Asn Pro Phe
420 425 430
Ile Cys Asp Cys His Leu Lys Trp Leu Ala Asp Tyr Leu His Thr Asn
435 440 445
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## <213> Rat

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 Ser
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 Met
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 His
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 Glu

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 5
 10
 15

 Leu
 Leu
 Phe
 Cys
 Phe
 Ser
 Leu
 Phe
 Leu
 Trp

 Phe
 Cys
 Phe
 Leu
 Phe
 Leu
 Phe
 Asp
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 Pro

 Met
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Ser Leu Asn Ile Ala Ala Ser Ala Ala Val Gln Ala Ala Thr Lys Ser 135 Gln Gly Ala Leu Ala Gly Arg Leu Arg Ser Phe Ser Met Gln Asp Leu 145 150 155 160 Arg Ser Ile Pro Asp Thr Pro Val Pro Thr Tyr Gln Asp Pro Leu Tyr 165 170 175 Leu Glu Asp Gln Val Pro Arg Arg Pro Pro Ile Gly Tyr Arg Pro 180 185 190 180 185 Gly Gly Leu Gln Gly Ser Asp Thr Glu Asp Glu Cys Trp Ser Asp Asn 195 200 205 Glu Ile Val Pro Gln Pro Pro Val Gly Pro Arg Glu Lys Pro Leu Gly 210 215 220 Arg Ser Gln Ser Leu Arg Val Val Lys Arg Lys Pro Leu Thr Arg Glu 225 230 235 240 Gly Thr Ser Arg Ser Leu Lys Val Arg Thr Pro Lys Lys Ala Met Pro 245 250 255 250 Ser Asp Met Asp Ser 260

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Ala Ala Gly Asp Met Val Tyr Thr Leu Gln Leu Glu Asp Arg Asn Lys
100 105 110
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115 120 125
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130 . 135 140
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145 150 155 160
Lys Ser Val Pro Pro Thr Leu Lys Ala Pro Arg Val Thr Gln Leu Glu
165 170 175
 Gly Asm Ser Cys Glu Ile Phe Trp Glu Thr Val Pro Pro Met Arg Gly
180 185 190
 Asp Pro Val Ser Tyr Val Leu Gln Val Leu Val Gly Arg Asp Ser Glu
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 Tyr Lys Gln Val Tyr Lys Gly Glu Glu Ala Thr Phe Gln Ile Ser Gly 210 215 220
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225 230 235 240
 Cys Val Asp Thr Ser Gln Glu Leu Ser Gly Ala Phe Ser Pro Ser Ala
245 250 255
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1020

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1080

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Lys Ile Arg Tyr Ser Asp Val Lys Lys Leu Glu Met Lys Pro Lys Tyr
35 40 45
Pro His Cys Glu Glu Lys Met Val Ile Val Thr Thr Lys Ser Met Ser 50 55 60
Arg Tyr Arg Gly Gln Glu His Cys Leu His Pro Lys Leu Gln Ser Thr
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Tyr Glu Glu
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cacggagece tagectggtt ccaccaccag cgacgccgta tectgcagga gggtggcgtg
                                                                      1680
gtaatcette tettetegee egeggeegtg gegeagtgte ageagtgget geageteeag
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acagtggage cegggeegea tgaegeeete geegeetgge teagetgegt gefaceegat
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coggetttee tggatgeact geagggagge tgetecaett cegeggggeg accegeggae
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      <213> Rati
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Glu Gly Leu Cys Arg Leu Trp Thr Ala Thr Cys His Ser Arg Gly Glu 35 40 45
Ser Glu Val Ser Arg Ser Ser Arg Lys Glu Asp Pro Arg Ile Pro Gln 50 55 60
Gly Ser Leu Ser Gly Asn Val Asp Phe Trp Arg Val Cys Pro Pro Cys 65 70 75 80
Ala His Thr Ser Met Asp Arg Thr Leu Gly Leu Leu Ser Cys Cys
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20 25 30
Leu Thr Leu Ile Val Cys His Ile Asn Ser Pro Gly Cys Val Phe Phe 35 40 45
Ser Arg Lys Lys beu Lys Gly Lys Thr Lys Pro Lys Lys Pro Glu Thr 50 55 60
Thr Asn Lys Asn Gly Asn Asp Asn Gly Cys Leu Ser Phe Phe Cys His 65 70 75 80
Asp Phe Pro Asp Leu Val Cys Ser Leu Cys Leu Arg Glu Ala Gly Asp 85 90 95
Val Asp Glu Ala Val Phe Phe Phe Leu Phe Leu Val Phe Glu Thr Arg
Val Ser Leu Cys His Pro Gly Trp Ser Val Thr Trp His Asp Leu Ser
115 120 125
Ser Leu Gln Pro Leu Pro Pro Gly Phe Lys Arg Leu Ser Cys Leu Ser 130 135 140
Leu Leu Ser Ser Trp Asp Tyr Arg His Ala Pro Leu Cys Pro Asp Asn 145 150 150 160
Phe Phe Val Phe Leu Val Glu Thr Gly Phe His His Val Gly Gln Ala
165 170 175
Gly Leu Glu Leu Leu Thr Ser Gly Tyr Pro Pro Thr Leu Ala Ser Gln
180 185 190
Ser Ala Gly Ile Ile Gly Met Asn His Arg Ala Trp Pro Lys Met
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Met Ser Gl<br/>n Val Gl<br/>n Val Ile Leu Leu Thr Leu Val Ser Gl<br/>n Ser Val
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Gly Ile Ile Gly Met Ser His Cys Ile Lys Pro Val Lys Ser Ile Tyr
20 25 30
```

Ile Lys Leu Asp Cys Arg Lys Arg Asp Lys Thr Ser Leu Leu Phe 35 40 45

> Cys Pro Gln Gly Pro Arg Asn Pro Val Ser Lys Ala Pro His Gln Leu 55 Gln Cys Val Pro Val Ser Arg Val Pro Thr Gly Thr Glu Ser Ser Gly 70

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The Arg Ser. Trp Leu Thr Arg Lys His The Gln Arg Leu His Ala Ala 20 25 30 Ala Thr Val Ile Lys Arg Ala Trp Gln Lys Trp Arg Ile Arg Met Ala . 35 40 45 Cys Leu Ala Ala Lys Glu Leu Asp Gly Val Glu Glu Lys His Phe Ser 50 55 60 Gln Ala Pro Cys Ser Leu Ser Thr Ser Pro Leu Gln Thr Arg Leu Leu 65 70 75 80 Glu Ala Ile Ile Arg Leu Trp Pro Leu Gly Leu Val Leu Ala Asn Thr 85 90 95

10

Ala Met Gly Val Gly Ser Phe Gln Arg Lys Leu Val Val Trp Ala Cys 100 105 110

Leu Gln Leu Pro Arg Gly Ser Pro Ser Ser Tyr Thr Val Gln Thr Ala 115 120 125

Gln Asp Gln Ala Gly Val Thr Ser Ile Arg Ala Leu Pro Gln Gly Ser 130 135 140 Ile Lys Phe His Cys Arg Lys Ser Pro Leu Arg Tyr Ala Asp Ile Cys 145 150 155 160

Pro Glu Pro Ser Pro Tyr Ser Ile Thr Gly Phe Asn Gln Ile Leu 165 170 175 170

Glu Arg His Arg Leu Ile His Val Thr Ser Ser Ala Phe Thr Gly Leu 180 185

Gly

<210> 492

<211> 104

<212> PRT

<213> Human

Met Pro Pro Asn Pro His Leu Thr Leu Ile Leu Ile Thr Ala Leu Trp 10 Glu Ala Val Val Gly Gly Ser Leu Lys Pro Arg Arg Leu Arg Leu Glu 20 25 30 Cys Cys Thr Ile Ala Pro Leu His Ser Thr Ala Trp Ala Thr Glu Gly 35 45 40 Asp Pro Val Ser Lys Lys Arg Glu Thr Ala Val Ala Ile Ile Val Val 50 60 . Arg Asn Asn Thr Glu Arg Ser Leu Val Leu Ser Ala Gln Leu Phe Leu 65 70 75 80 Thr Val Ser Leu Cys Arg Thr Pro Gln Ser His Thr Arg Thr Trp Thr

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95
Leu Met Pro Ser Gly Gly Leu Thr
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Phe Tyr Leu His Thr Ser Phe Ser Arg Pro His Thr Gly Pro Pro Leu
20 25 30
Pro Thr Pro Gly Pro Asp Arg Asp Arg Glu Leu Thr Ala Asp Ser Asp
       35
                             40
Val Asp Glu Phe Leu Asp Lys Phe Leu Ser Ala Gly Val Lys Gln Ser 50 55 60
                                             60
Asp Leu Pro Arg Lys Glu Thr Glu Gln Pro Pro Ala Pro Gly Ser Met 65 70 75 80
Glu Glu Ser Val Arg Gly Tyr Asp Trp Ser Pro Arg Asp Ala Arg Arg
85 90 95
Ser Pro Asp Gln Gly Arg Gln Gln Ala Glu Arg Arg Ser Val Leu Arg
                                 105
                                                     110
Gly Phe Cys Ala Asn Ser Ser Leu Ala Phe Pro Thr Lys Glu Arg Ala
115 120 125
Phe Asp Asp Ile Pro Asn Ser Glu Leu Ser His Leu Ile Val Asp Asp
                      135
   130
                                      140
Arg His Gly Ala Ile Tyr Cys Tyr Val Pro Lys Val Ala Cys Thr Asn
145 150 155 160
Trp Lys Arg Val Met Ile Val Leu Ser Gly Ser Leu Leu His Arg Gly
165 170 175
Ala Pro Tyr Arg Asp Pro Leu Arg Ile Pro Arg Glu His Val His Asn 180 185 190
Ala Ser Ala His Leu Thr Phe Asn Lys Phe Trp Arg Arg Tyr Gly Lys
195 200 205
Leu Ser Arg His Leu Met Lys Val Lys Leu Lys Lys Tyr Thr Lys Phe 210 220
Leu Phe Val Arg Asp Pro Phe Val Arg Leu Ile Ser Ala Phe Arg Ser
225
                    230
                                         235
Lys Phe Glu Leu Glu Asn Glu Glu Phe Tyr Arg Lys Phe Ala
   <210> 494
      <211> 215
<212> PRT
      <213> Rat
      <400> 494 '
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                                 25
Val His Thr Pro Pro Leu Gly Pro Ile Leu Lys Lys Thr Ala Gly Leu 35 40 45
Gly Phe Cys Ala Val Phe Leu Tyr Phe Ile Thr Ala Leu Ile Phe Pro
                         55
                                               60
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Ala Ile Ser Thr Asn Ile Gln Pro Met His Lys Gly Thr Gly Ser Pro 65 70 75 80
Trp Thr Ser Lys Phe Tyr Val Pro Leu Thr Val Phe Leu Leu Phe Asn
                 85
                                       90 .
                                                            95
Phe Ala Asp Leu Cys Gly Arg Gln Val Thr Ala Trp Ile Gln Val Pro
           100
                      105
                                                    110
Gly Pro Arg Ser Lys Leu Leu Pro Ile Leu Ala Val Ser Arg Val Cys
115 120 125
Leu Val Pro Leu Phe Leu Leu Cys Asn Tyr Gln Pro Arg Ser His Leu 130 140
Thr Leu Val Leu Phe Gln Ser Asp Ile Tyr Pro Ile Leu Phe Thr Cys
145 150 155 160
Leu Leu Gly Leu Ser Asn Gly Tyr Leu Ser Thr Leu Val Leu Met Tyr
165 170 175
Gly Pro Lys Ile Val Pro Arg Glu Leu Ala Glu Ala Thr Ser Val Val
180 185 190
Met Leu Phe Tyr Met Ser Leu Gly Leu Met Leu Gly Ser Ala Cys Ala
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Ala Leu Leu Glu His Phe Ile
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<211> 91

<212> PRT

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<400> 495

<210> 496 <211> 224

<212> PRT

<213> Human

<400> 496

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 Ala
 Cys
 Gly
 Pro
 Gly
 Ala
 Ala
 Gly
 Tyr
 Cys
 Leu
 Leu
 Leu

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85
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Cys Lys Thr Asp Leu Asp Ile Ala Tyr Lys Phe Gly Lys Thr Val Val
          100
                          105
                                               110
Ser Cys Glu Gly Tyr Glu Ser Ser Glu Asp Gln Tyr Val Leu Arg Gly
115 120 125
                                           125
Ser Cys Gly Leu Glu Tyr Asn Leu Asp Tyr Thr Glu Leu Gly Leu Gln
130 135 140
Tyr Tyr Tyr Lys Trp Ser Ser Ala Asp Ser Cys Asn Met Ser Gly Leu
165 170 175
Ile Thr Ile Val Val Leu Leu Gly Ile Ala Phe Val Val Tyr Lys Leu
180 185 190
Phe Leu Ser Asp Gly Gln Tyr Ser Pro Pro Pro Tyr Ser Glu Tyr Pro
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                        200
                                          205
Pro Phe Ser His Arg Tyr Gln Arg Phe Thr Asn Ser Ala Gly Pro Pro
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<211> 766

<212> PRT

<213> Rat

<400> 497

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260
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Gln Trp Arg Arg Gly Leu Trp Val Arg Arg Pro His Asp Ser Thr Gln
                              280
                                                       285
Leu Leu Thr Gly Arg Thr Phe Gln Gly Thr Thr Val Gly Leu Ala Pro
290 295 300
Val Glu Gly Met Cys His Ala Glu Ser Ser Gly Gly Val Ser Thr Asp
305 310 315 320
His Ser Glu Leu Pro Ile Glỳ Thr Ala Ala Thr Met Ala His Glu Ile
325 330 335
Gly His Ser Leu Gly Leu His His Asp Pro Glu Gly Cys Cys Met Glu
340 345 350
Ala Asp Ala Glu Gln Gly Gly Cys Val Met Glu Ala Ala Thr Gly His
355 360 365
Pro Phe Pro Arg Val Phe Ser Ala Cys Ser Arg Arg Gln Leu Arg Thr 370 375 380
Phe Phe Arg Lys Gly Gly Gly Ala Cys Leu Ser Asn Val Ser Ala Pro
385 390 395 400
Gly Leu Leu Val Leu Pro Ser Arg Cys Gly Asn Gly Phe Val Glu Ala
405 410 415
Glu Glu Glu Cys Asp Cys Gly Ser Gly Gln Lys Arg Pro Asp Pro Cys
420 425 430
Cys Phe Ala His Asn Cys Ser Leu Arg Ala Gly Ala Gln Cys Ala Gln
435 440 445
Gly Asp Cys Cys Ala Arg Cys Leu Leu Lys Pro Ala Gly Thr Pro Cys
450 455 460
Arg Pro Ala Ala Asn Asp Cys Asp Leu Pro Glu Phe Cys Thr Gly Thr 465 470 475 480
Ser Pro His Cys Pro Ala Asp Val Tyr Leu Leu Asp Gly Ser Pro Cys
485 490 495
Ala Glu Gly Arg Gly Tyr Cys Leu Asp Gly Trp Cys Pro Thr Leu Glu 500 505 . 510
Lys Gln Cys Gln Gln Leu Trp Gly Pro Gly Ser Gln Pro Ala Pro Glu
515 520 525
Pro Cys Phe Gln Gln Met Asn Ser Val Gly Asn Ser Gln Gly Asn Cys
530 535 540
Gly Gln Asp Ser Lys Gly Ser Phe Leu Pro Cys Thr Gln Arg Asp Ala
545 550 555 560
Gln Cys Gly Lys Leu Leu Cys Gln Gly Gly Lys Pro Asn Pro Leu Val
565 570 575
Pro His Val Val Thr Val Asp Ser Thr Ile Leu Leu Glu Gly Arg Gln 580 595
Val Leu Cys Arg Gly Ala Phe Val Leu Pro Asp Thr His Leu Asp Gln 595 600 605
Leu Gly Leu Gly Leu Val Glu Pro Gly Thr Arg Cys Gly Pro Arg Met 610 615 620
Val Cys Gln Glu Arg His Cys Gln Asn Ala Thr Ser Gln Glu Leu Glu 625 630 . 635 . 640
Arg Cys Ser Ser Gly Cys His Asn Arg Gly Val Cys Asn Ser Asn Arg 645 650 655
Asn Cys His Cys Ala Ala Gly Trp Ala Pro Pro Phe Cys Asp Lys Pro 660 665 670
Gly Leu Gly Gly Ser Val Asp Ser Gly Pro Ala Gln Ser Ala Asn Pro 675 680 685
Asp Ala Phe Pro Leu Ala Met Leu Ser Phe Leu Leu Pro Leu Leu 690 695 700
Pro Gly Ala Gly Leu Ala Trp Cys Tyr Tyr Gln Leu Pro Thr Leu Cys
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                                               715
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Gln Gln Pro Gly Arg Cys Cys Arg Arg Asp Ala Leu Cys Asn Arg Asp 725 730 735
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Gly Glu Pro Ser Pro Pro Asn Pro Glu Glu Ser Glu Leu Thr
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Ala Glu Asp Val Lys Arg Pro Pro Glu Pro Leu Val Thr Asp Lys Glu 35 40 45
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Ala Arg Lys Lys Val Leu Lys Gln Ala Phe Ser Val Ser Arg Val Pro 50 55 60
Glu Lys Leu Asp Ala Val Val Ile Gly Ser Gly Ile Gly Gly Leu Ala
65 70 75 80
Ser Ala Ala Ile Leu Ala Lys Ala Gly Lys Arg Val Leu Val Leu Glu
                85
                                     90
Gln His Thr Lys Ala Gly Gly Cys Cys His Thr Phe Gly Glu Asn Gly 100 105 110
Leu Glu Phe Asp Thr Gly Ile His Tyr Ile Gly Arg Met Arg Glu Gly 115 120 125
Asn Ile Gly Arg Phe Ile Leu Asp Gln Ile Thr Glu Gly Gln Leu Asp
130 135 140
                                              140
Trp Ala Pro Met Ala Ser Pro Phe Asp Leu Met Ile Leu Glu Gly Pro 145 150 155 160
                                                                 160
Asn Gly Arg Lys Glu Phe Pro Met Tyr Ser Gly Arg Lys Glu Tyr Ile
165 170 175
Gln Gly Leu Lys Glu Lys Phe Pro Lys Glu Glu Ala Val Ile Asp Lys
180 185 190
Tyr Met Glu Leu Val Lys Val Val Ala His Gly Val Ser His Ala Ile
       195 200 205
Leu Leu Lys Phe Leu Pro Leu Pro Leu Thr Gln Leu Leu Asn Lys Phe 210 220
Gly Leu Leu Thr Arg Phe Ser Pro Phe Cys Arg Ala Ser Thr Gln Ser 225 230 240
Leu Ala Glu Val Leu Lys Gln Leu Gly Ala Ser Pro Glu Leu Gln Ala
245 250 255
Val Leu Ser Tyr Ile Phe Pro Thr Tyr Gly Val Thr Pro Ser His Thr 260 265 270
Thr Phe Ser Leu His Ala Leu Leu Val Asp His Tyr Ile Gln Gly Ala
275 280 285
Tyr Tyr Pro Arg Gly Gly Ser Ser Glu Ile Ala Phe His Thr Ile Pro
290 295 300
Leu Ile Gln Arg Ala Gly Gly Ala Val Leu Thr Arg Ala Thr Val Gln 305 . 310 315 . 320
Ser Val Leu Leu Asp Ser Ala Gly Arg Ala Cys Gly Val Ser Val Lys
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                                   330
                                                           335
Lys Gly Gln Glu Leu Val Asn Ile Tyr Cys Pro Val Val Ile Ser Asn
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                                  345
                                                        350
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Ala Gly Met Phe Asn Thr Tyr Gln His Leu Leu Pro Glu Ser Val Arg
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                               360
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Tyr Leu Pro Asp Val Lys Lys Gln Leu Thr Met Val Lys Pro Gly Leu
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    370
Ser Met Leu Ser Ile Phe Ile Cys Leu Lys Gly Thr Lys Glu Glu Leu
385 390 395 400
Lys Leu Gln Ser Thr Asn Tyr Tyr Val Tyr Phe Asp Thr Asp Met Asp
405 410 415
Lys Ala Met Glu Arg Tyr Val Ser Met Pro Lys Glu Lys Ala Pro Glu
420 425 430
                                                         430
His Ile Pro Leu Leu Phe Ile Ala Phe Pro Ser Ser Lys Asp Pro Thr
435 440 445
Trp Glu Asp Arg Phe Pro Asp Arg Ser Thr Met Thr Val Leu Val Pro 450 455 460
Thr Ala Phe Glu Trp Phe Glu Glu Trp Gln Glu Glu Pro Lys Gly Lys 465 470 475 480
                                         475
Arg Gly Val Asp Tyr Glu Thr Leu Lys Asn Thr Phe Leu Glu Ala Ser
485 490 495
Met Ser Val Ile Met Lys Leu Phe Pro Gln Leu Glu Gly Lys Val Glu 500 505 510
Ser Val Thr Gly Gly Ser Pro Leu Thr Asn Gln Tyr Tyr Leu Ala Ala
515 520 525
His Arg Gly Ala Thr Tyr Gly Ala Asp His Asp Leu Ala Arg Leu His 530 540
Pro His Ala Met Ala Ser Leu Arg Ala Gln Thr Pro Ile Pro Asn Leu
545 550 555 560
Tyr Leu Thr Gly Gln Asp Ile Phe Thr Cys Gly Leu Met Gly Ala Leu 565 570 575
Gln Gly Ala Leu Leu Cys Ser Ser Ala Ile Leu Lys Arg Asn Leu Tyr
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Ser Asp Leu Gln Ala Leu Gly Ser Lys Val Arg Ala Gln Lys Lys
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Lys
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 Phe
 Gly
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 Tyr
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 Asp
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 Gly
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 Asp
 Asp
 Asp
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 Asp
 Asp
 Asp

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Ser Val Arg Asp Gln Asp Ser Gly Asp Asn Gly Arg Ile Leu Cys Ser
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                           135
Ile Pro Asp Asp Leu Pro Phe Ile Leu Lys Pro Thr Phe Lys Asn Phe 145 150 155 160
Phe Thr Leu Leu Ser Glu Lys Ala Leu Asp Arg Glu Ser Arg Ala Glu
165 170 175
Tyr Asn Ile Thr Ile Thr Val Ser Asp Leu Gly Thr Pro Arg Leu Thr
180 ' 185 190
Thr Gln His Thr Ile Thr Val Gln Val Ser Asp Ile Asn Asp Asn Ala
195 200 205
Pro Ala Phe Thr Gln Thr Ser Tyr Thr Met Phe Val His Glu Asn Asn 210 215 220
Ser Pro Ala Leu His Ile Gly Thr Ile Ser Ala Thr Asp Ser Asp Ser 225 230 235 240
Gly Ser Asn Ala His Ile Thr Tyr Ser Leu Met Pro Pro Arg Asp Pro
245 250 255
Gln Leu Ala Leu Asp Ser Leu Ile Ser Ile Asn Ala Asp Asn Gly Gln
260 265 270
Leu Phe Ala Leu Arg Ala Leu Asp Tyr Glu Val Leu Gln Ala Phe Glu 275 280 285
Phe Arg Val Gly Ala Thr Asp Arg Gly Ser Pro Ala Leu Ser Ser Gln
290 295 300
Ala Leu Val Arg Val Val Leu Asp Asp Asn Asp Asn Ala Pro Phe 305 310 315 320
Val Leu Tyr Pro Leu Gln Asn Ala Ser Ala Pro Tyr Thr Glu Leu Leu 325 330 335
Pro Arg Ala Ala Glu Pro Gly Tyr Leu Val Thr Lys Val Val Ala Val 340 345 350
Asp Arg Asp Ser Gly Gln Asn Ala Trp Leu Ser Phe Gln Leu Leu Lys
355 360 365
Ala Thr Glu Pro Gly Leu Phe Ser Val Trp Ala His Asn Gly Glu Val 370 380
Arg Thr Ser Arg Leu Leu Ser Glu Arg Asp Ala Pro Lys His Lys Leu
385 390 395 400
Leu Leu Met Val Lys Asp Asn Gly Asp Pro Pro Arg Ser Ala Ser Val
. 405 410 415
Met Leu His Val Leu Val Val Asp Gly Phe Ser Gln Pro Tyr Leu Pro
420 425 430
Leu Pro Glu Val Ala His Asn Pro Ala His Asp Glu Asp Thr Leu Thr
435 440 445
Leu Tyr Leu Val Ile Ala Leu Ala Ser Val Ser Ser Leu Phe Leu Leu 450 455 460
Ser Val Leu Leu Phe Val Gly Val Arg Leu Cys Lys Lys Ala Arg Ala 465 470 480
Ala Ser Leu Gly Gly Cys Ser Val Pro Glu Gly His Phe Pro Gly His
485 490 495 .
Leu Val Asp Val Thr Gly Thr Gly Thr Leu Ser Gln Asm Tyr Gln Tyr 500 505 510
Glu Val Cys Leu Thr Gly Ser Thr Gly Thr Asn Glu Phe Lys Phe Leu 515 520 525
Lys Pro Val Met Pro Ser Leu Gln Leu Gln Asp Pro Asp Ser Asn Met
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Leu Val Lys Glu Asn Phe Arg Asn Ser Leu Gly Phe Asn Ile Gln
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130 135 140 Val Pro Asp Leu Val Leu Asp Ala Arg Ser Asp Leu Pro Thr Ala Met 145 150 155 160 Glu Tyr Cys Gln Gln Val Leu Arg Arg Pro Ala Gln Asp Cys Ser Ser 165 170 175 Tyr Thr Leu Ser Phe Asp Thr Thr Val Phe Ile Ile Glu Ser Thr Arg 180 185 190 Arg Arg Val Ala Val Glu Ala Thr Leu Glu Asn Arg Gly Glu Asn Ala 195 200 205 Tyr Ser Ala Val Leu Asn Ile Ser Gln Ser Glu Asn Leu Gln Phe Ala 210 215 220 Ser Leu Ile Gln Lys Asp Asp Ser Asp Asp Ser Ile Glu Cys Val Asn 225 230 235 240 Glu Glu Arg Arg Leu His Lys Lys Val Cys Asn Val Ser Tyr Pro Phe . 245 250 255 Phe Arg Ala Lys Ala Lys Val Ala Phe Arg Leu Asp Phe Glu Phe Ser 260 265 270 Lys Ser Val Phe Leu His His Leu Gln Ile His Leu Gly Ala Gly Ser 275 280 285 Asp Ser His Glu Gln Asp Ser Thr Ala Asp Asp Asn Thr Ala Leu Leu 290 295 300 Arg Phe His Leu Lys Tyr Glu Ala Asp Val Leu Phe Thr Arg Ser Ser 305 310 315 320 Ser Leu Ser His Phe Glu Val Lys Ala Asn Ser Ser Leu Glu Ser Tyr 325 330 335 Asp Gly Ile Gly Pro Pro Phe Asn Cys Val Phe Lys Val Gln Asn Leu 340 345 350 Gly Phe Phe Pro Ile His Gly Val Met Met Lys Ile Thr Val Pro Ile 355 360 365 Ala Thr Arg Gly Gly Asn Arg Leu Leu Met Leu Lys Asp Phe Phe Thr 370 375 380 380 Asp Gln Val Asn Thr Ser Cys Asn Ile Trp Gly Asn Ser Thr Glu Tyr 385 390 395 400 Arg Ser Thr Pro Thr Glu Glu Asp Leu Ser His Ala Pro Gln Arg Asn 410 His Ser Asn Ser Asp Val Val Ser Ile Ile Cys Asn Val Arg Leu Ala

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425
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Pro Asn Gln Glu Thr Ser Phe Tyr Leu Val Gly Asn Leu Trp Leu Met
                      440
                                                     445
Ser Leu Lys Ala Leu Lys Tyr Arg Ser Met Lys Ile Thr Val Asn Ala 450 455 460
Ala Leu Gln Arg Gln Phe His Ser Pro Phe Ile Phe Arg Glu Glu Asp 465 470 475 480
Pro Ser Arg Gln Val Thr Phe Glu Ile Ser Lys Gln Glu Asp Trp Gln
485 490 495
Val Pro Ile Trp Ile Ile Val Gly Ser Ser Leu Gly Gly Leu Leu Leu 500 505 510
Leu Ala Leu Leu Val Leu Ala Leu Trp Lys Leu Gly Phe Phe Lys Ser 515 520 525
Ala Lys Arg Lys Arg Glu Pro Ser Leu Gly Pro Val Pro Lys Glu Leu
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Glu
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Val Gln Asp Leu Asn Gln Asp Ser Tyr Asn Asp Val Val Gly Ala
50 55 60
Pro Leu Glu Asp Ser His Arg Gly Ala Ile Tyr Ile Phe His Gly Phe 65 70 75 80
Gln Thr Asn Ile Leu Lys Lys Pro Val Gln Arg Ile Ser Ala Ser Glu
. 85 90 95
Leu Ala Pro Gly Leu Gln His Phe Gly Cys Ser Ile His Gly Gln Leu
100 105 110
Asp Leu Asn Glu Asp Gly Leu Val Asp Leu Ala Val Gly Ala Leu Gly
115 120 125
Asn Ala Val Val Leu Trp Ala Arg Pro Val Val Gln Ile Asn Ala Ser
130 135 140 .
Leu His Phe Glu Pro Ser Lys Ile Asn Ile Phe His Lys Asp Cys Lys 145 150 155 160
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Pro Asp His Gly Pro Met Leu Asp Asn Gly Trp Pro Thr Thr Leu Arg

Arg Asn Gly Arg Asp Ala Thr Cys Leu Ala Ala Phe Leu Cys Phe Gly 165 170 175

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Val Ser Val Pro Phe Trp Asn Gly Cys Asn Glu Asp Glu His Cys Val
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                             280
                                                     285
Pro Asp Leu Val Leu Asp Ala Arg Ser Asp Leu Pro Thr Ala Met Glu
290 295 300
Tyr Cys Gln Gln Val Leu Arg Arg Pro Ala Gln Asp Cys Ser Ser Tyr 305 310 315 320
Thr Leu Ser Phe Asp Thr Thr Val Phe Ile Ile Glu Ser Thr Arg Arg 325 330 335
Arg Val Ala Val Glu Ala Thr Leu Glu Asn Arg Gly Glu Asn Ala Tyr
340 345 350
Ser Ala Val Leu Asn Ile Ser Gln Ser Glu Asn Leu Gln Phe Ala Ser
355 360 365
Leu Ile Gin Lys Asp Asp Ser Asp Asn Ser Ile Glu Cys'Val Asn Glu 370 375 380
Glu Arg Arg Leu His Lys Lys Val Cys Asn Val Ser Tyr Pro Phe Phe
                  390
                                            395
Arg Ala Lys Ala Lys Val Ala Phe Arg Leu Asp Phe Glu Phe Ser Lys
405 410 415
                                        410
Ser Val Phe Leu His His Leu Gln Ile His Leu Gly Ala Gly Ser Asp
            420
                                   425
                                                          430
Ser His Glu Gln Asp Ser Thr Ala Asp Asp Asn Thr Ala Leu Leu Arg
435 440 445
Phe His Leu Lys Tyr Glu Ala Asp Val Leu Phe Thr Arg Ser Ser Ser 450 455 460
                         455
                                        460
Leu Ser His Phe Glu Val Lys Ala Asn Ser Ser Leu Glu Ser Tyr Asp
465 470 475 480
                                          475
Gly Ile Gly Pro Pro Phe Asn Cys Val Phe Lys Val Gln Asn Leu Gly
485 490 495
Phe Phe Pro Ile His Gly Val Met Met Lys Ile Thr Val Pro Ile Ala 500 505 510
Thr Arg Gly Gly Asn Arg Leu Leu Met Leu Lys Asp Phe Phe Thr Asp 515 520 525
Gln Val Asn Thr Ser Cys Asn Ile Trp Gly Asn Ser Thr Glu Tyr Arg
530 535 540
                                              540
Ser Thr Pro Thr Glu Glu Asp Leu Ser His Ala Pro Gln Arg Asn His 545 550 555 555
Ser Asn Ser Asp Val Val Ser Ile Ile Cys Asn Val Arg Leu Ala Pro
565 570 575
Asn Gln Glu Thr Ser Phe Tyr Leu Val Gly Asn Leu Trp Leu Met Ser 580 585 590
Leu Lys Ala Leu Lys Tyr Arg Ser Met Lys Ile Thr Val Asn Ala Ala
595 600 605
Leu Gln Arg Gln Phe His Ser Pro Phe Ile Phe Arg Glu Glu Asp Pro 610 615 620
                                                620
Ser Arg Gln Val Thr Phe Glu Ile Ser Lys Gln Glu Asp Trp Gln Val
625 630 635 . 640
                                           635 . .
Pro Ile Trp Ile Ile Val Gly Ser Ser Leu Gly Gly Leu Leu Leu Leu 645 650 655
Ala Leu Leu Val Leu Ala Leu Gly Ser Leu Val Ser Leu Lys Val Pro
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Ser Ala Arg Gly Ser Pro Ala Trp Ala Pro Ser Pro Lys Ser Trp Ser 675 680 685
Glu Asp Pro Glu Glu Ala Ser Ser
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<210> 502

<211> 242 <212> PRT <213> Rat

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<210> 503 <211> 819 <212> PRT <213> Rat

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105
Glu Met Asp Ser Arg Leu Ala Gln Pro Thr Ser Ala Ser Leu Pro Glu
115 120 125
Thr Thr Val Ala Val Pro Pro Thr Pro Ala Gln Arg Lys Gly Lys Asn
130 135 140
Ser Val Ala Val Met Ser Arg Leu Phe Asp Met Ser Cys Asp Glu Thr
145 150 155 160
Leu Cys Ser Ala Asp Ser Phe Cys Val Asn Asp Tyr Ala Trp Gly Gly
165 170 175
Ser Arg Cys His Cys Asn Leu Gly Lys Gly Gly Glu Ala Cys Ser Glu
180 185 190
Asp Ile Phe Ile Gln Tyr Pro Gln Phe Phe Gly His Ser Tyr Val Thr
195 200 205
Phe Glu Pro Leu Lys Asn Ser Tyr Gln Ala Phe Gln Ile Thr Leu Glu
210 215 220
Phe Arg Ala Glu Ala Glu Asp Gly Leu Leu Leu Tyr Cys Gly Glu Ser 225 230 235 240
Glu His Gly Arg Gly Asp Phe Met Ser Leu Ala Leu Ile Arg Arg Ser 245 250 255
Leu His Phe Arg Phe Asn Cys Gly Thr Gly Met Ala Ile Ile Ile Ser
260 265 270
Glu Thr Lys Ile Lys Leu Gly Ala Trp His Ser Val Thr Leu Tyr Arg
        275 ·
                              280
                                                      285
Asp Gly Leu Asn Gly Leu Leu Gln Leu Asn Asn Gly Thr Pro Val Thr 290 295 300
Gly Gln Ser Gln Gly Gln Tyr Ser Lys Ile Thr Phe Arg Thr Pro Leu 305 310 315 320
Tyr Leu Gly Gly Ala Pro Ser Ala Tyr Trp Leu Val Arg Ala Thr Gly 325 330 335
Thr Asn Arg Gly Phe Gln Gly Cys Val Gln Ser Leu Ala Val Asn Gly 340 345 350
Lys Lys Ile Asp Met Arg Pro Trp Pro Leu Gly Lys Ala Leu Asn Gly 355 360 365
Ala Asp Val Ġly Glu Cys Ser Ser Gly Ile Cys Asp Glu Ala Ser Cys 370 380
Ile Asn Gly Gly Thr Cys Ala Ala Ile Lys Ala Asp Ser Tyr Ile Cys
385 390 395 400
Leu Cys Pro Leu Gly Phe Arg Gly Arg His Cys Glu Asp Ala Phe Thr
405 410 415
Leu Thr Ile Pro Gln Phe Arg Glu Ser Leu Arg Ser Tyr Ala Ala Thr 420 425 430
Pro Trp Pro Leu Glu Pro Gln His Tyr Leu Ser Phe Thr Glu Phe Glu 435 440 445
Ile Thr Phe Arg Pro Asp Ser Gly Asp Gly Val Leu Leu Tyr Ser Tyr 450 455 460
                                                 460
Asp Thr Ser Ser Lys Asp Phe Leu Ser Ile Ile Met Ala Ala Gly His 465 470 475 480
Val Glu Phe Arg Phe Asp Cys Gly Ser Gly Thr Gly Val Leu Arg Ser
485 490 495
Glu Asp Thr Leu Thr Leu Gly Gln Trp His Asp Leu Arg Val Ser Arg 500 505 510
Thr Ala Lys Asn Gly Ile Leu Gln Val Asp Lys Gln Lys Val Val Glu
515 520 525
Gly Met Ala Glu Gly Gly Phe Thr Gln Ile Lys Cys Asn Thr Asp Ile 530 540
Phe Ile Gly Gly Val Pro Asn Tyr Asp Asp Val Lys Lys Asn Ser Gly
                       550
                                              555
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Ile Leu His Pro Phe Ser Gly Ser Ile Gln Lys Ile Ile Leu Asn Asp 565 570 575 Arg Thr Ile His Val Arg His Asp Phe Thr Ser Gly Val Asn Val Glu 580 585 590 585 Asn. Ala Ala His Pro Cys Val Gly Ala Pro Cys Ala His Gly Gly Ser 595 600 605 Cys Arg Pro Arg Lys Glu Gly Tyr Glu Cys Asp Cys Pro Leu Gly Phe 610 615 620 Glu Gly Leu Asn Cys Gln Lys Ala Ile Thr Glu Ala Ile Glu Ile Pro 625 630 635 640 Gln Phe Ile Gly Arg Ser Tyr Leu Thr Tyr Asp Asn Pro Asn Ile Leu 645 650 655 Lys Arg Val Ser Gly Ser Arg Ser Asn Ala Phe Met Arg Phe Lys Thr 660 665 670 Thr Ala Lys Asp Gly Leu Leu Leu Trp Arg Gly Asp Ser Pro Met Arg 675 680 685 Pro Asn Ser Asp Phe Ile Ser Leu Gly Leu Arg Asp Gly Ala Leu Val 690 695 700 Phe Ser Tyr Asn Leu Gly Ser Gly Val Ala Ser Ile Met Val Asn Gly 705 710 715 720 Ser Phe Ser Asp Gly Arg Trp His Arg Val Lys Ala Val Arg Asp Gly 725 730 735 Gln Ser Gly Lys Ile Thr Val Asp Asp Tyr Gly Ala Arg Thr Gly Lys 740 745 750 Ser Pro Gly Met Met Arg Gln Leu Asn Ile Asn Gly Ala Leu Tyr Val 755 760 765 Gly Gly Met Lys Glu Ile Ala Leu His Thr Asn Arg Gln Tyr Met Arg 770 775 780 Gly Leu Val Gly Cys Ile Ser His Phe Thr Leu Ser Thr Asp Tyr His 790 795 Ile Ser Leu Val Glu Asp Ala Val Asp Gly Lys Asn Ile Asn Thr Cys 805 810 Gly Ala Lys .

<210> 504 <211> 127 <212> PRT <213> Rat

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 504

 Gly
 Glu
 Pro
 Lys
 Gly
 Gly
 Gly
 Gly
 Arg
 Ala
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 Gly
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 Gly
 Arg
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Glu Asn Tyr Glu Glu Thr Ala Ala Ala Leu His Ala Leu Pro Gly Leu
                             40
       35
Arg Arg Leu Asp Leu Ser Gly Asn Ala Leu Thr Glu Asp Met Ala Ala 50 55 60
Leu Met Leu Gln Asn Leu Ser Ser Leu Arg Ser Val Ser Leu Ala Gly 65 70 75 80
Asn Thr Ile Met Arg Leu Asp Asp Ser Val Phe Glu Gly Leu Glu Arg 85 90 95
Leu Arg Glu Leu Asp Leu Gln Arg Asn Tyr Ile Phe Glu Ile Glu Gly
100 105 110
Gly Ala Phe Asp Gly Leu Ala Glu Leu Arg His Leu Asn
                              120
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Ala Gly Gly Val Gly Thr Ser Pro Arg Asp Tyr Trp Leu Pro Ala Leu
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Ala His Gln Pro Gly Val Cys His Tyr Gly Thr Lys Thr Ala Cys Cys 35 40 45
Tyr Gly Trp Lys Arg Asn Ser Lys Gly Val Cys Glu Ala Val Cys Glu
50 60
Pro Arg Cys Lys Phe Gly Glu Cys Val Gly Pro Asn Lys Cys Arg Cys 65 70 75 80
Phe Pro Gly Tyr Thr Gly Lys Thr Cys Ser Gln Asp Val Asn Glu Cys
                .85
                                     90
Ala Phe Lys Pro Arg Pro Cys Gln His Arg Cys Val Asn Thr His Gly
100 105 110
Ser Tyr Lys Cys Phe Cys Leu Ser Gly His Met Leu Leu Pro Asp Ala
115 120 125
Thr Cys Ser Asn Ser Arg Thr Cys Ala Arg Ile Asn Cys Gln Tyr Ser 130 135 140
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PCT/NZ01/00099 WO 01/90357

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215
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Thr Arg Thr Cys Ser Pro His Ala Asn Cys Leu Asn Thr Gln Gly Ser 225 230 235 240
Phe Lys Cys Lys Cys Lys Gln Gly Tyr Arg Gly Asn Gly Leu Gln Cys 245 . 250 255
Ser Val Ile Pro Glu His Ser Val Lys Glu Ile Leu Thr Ala Pro Gly
260 265 270
Thr Ile Lys Asp Arg Ile Lys Lys Leu Leu Ala His Lys His Thr Met 275 280 285
Lys Lys Lys Val Lys Leu Lys Asn Val Thr Pro Arg Pro Thr Ser Thr 290 295 300
Arg Ala Pro Lys Val Asn Leu Pro Tyr Ser Ser Glu Glu Gly Val Ser 305 310 315 320
Arg Gly Arg Asn Ser Gly Glu Glu Glu Lys Arg Lys Glu Glu Arg Lys
325 330 335
Arg Lys Arg Leu Glu Glu Glu Lys Ser Glu Lys Ala Leu Arg Asn Glu 340 345 350
Val Glu Glu Arg Pro Leu Arg Gly Asp Val Phe Ser Pro Lys Val
355 360 365
Asn Glu Ala Glu Asp Leu Asp Leu Val Tyr Ile Gln Arg Lys Glu Leu
370 375 ... 380
Asn Ser Lys Gln Glu His Lys Ala Asp Leu Asn Ile Ser Val Asp Cys 385 390 395 400
Ser Phe Asp Leu Gly Val Cys Asp Trp Lys Gln Asp Arg Glu Asp Asp 405 410 415
Phe Asp Trp Asn Pro Ala Asp Arg Asp Asn Asp Val Gly Tyr Tyr Met 420 425 430
Ala Val Pro Ala Leu Ala Gly His Lys Lys Asn Ile Gly Arg Leu Lys
435 440 445
Leu Leu Leu Pro Asn Leu Thr Pro Gln Ser Asn Phe Cys Leu Leu Phe 450 455 460
Asp Tyr Arg Leu Ala Gly Asp Lys Val Gly Lys Leu Arg Val Phe Val 465 470 475 480
Lys Asn Ser Asn Asn Ala Leu Ala Trp Glu Glu Thr Lys Thr Glu Asp
485 490 495
Gly Lys Trp Lys Thr Gly Lys Val Pro Leu Tyr Gln Gly Ile Asp Thr 500 505 510
Thr Lys Ser Val Ile Phe Glu Ala Glu Arg Gly Lys Gly Lys Thr Gly 515 520 525
Glu Ile Ala Val Asp Gly Val Leu Leu Val Ser Gly Leu Cys Pro Asp
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Asp Phe Leu Ser Glu Glu Gly
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<211> 244

<212> PRT

<213> Mouse

<400> 507

Tyr Ala Ser Ala Ser Glu Pro Thr Glu Ile Tyr Arg Thr Glu Leu Gln 1 5 10 15 Gly Leu Trp Ile Asn Asp Ile Val Pro Ile Gly Arg Ile Gln Glu Pro
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55
                                                    60
Ser Ile Leu Ser Met Leu Tyr Glu Gly Asp Arg Lys Val Leu Tyr Asp 65 70 75 80
Leu Met Asn Met Leu Glu Leu Asn Gln Leu Gly His Met Asp Gly Pro 85 90 95
Gly Gly Lys Ile Leu Asp Glu Leu Arg Lys Asp Ser Ser Asn Pro Cys
100 105 110
Val Asp Leu Lys Asp Leu Ilè Leu Tyr Leu Leu Gln Ala Leu Met Val
115 120 125
Leu Ser Asp Ser Gln Leu Asn Leu Leu Ala Gln Ser Val Glu Met Gly 130 135 140
                                               140
Ile Leu Pro His Gln Val Glu Leu Val Lys Ser Ile Leu Gln Pro Asn
145 150 150 155 160
Phe Lys Tyr Pro Trp Asn Ile Pro Phe Thr Val Gln Pro Gln Leu Leu
165 170 175
Ala Pro Leu Gln Gly Glu Gly Leu Ala Ile Thr Tyr Glu Leu Leu Glu
180 185 190
Glu Cys Gly Leu Lys Met Glu Leu Asn Asn Pro Arg Ser Thr Trp Asp
195 200 205
Leu Glu Ala Lys Met Pro Leu Ser Ala Leu Tyr Gly Ser Leu Ser Phe 210 215 220
Leu Gln Gln Leu Arg Lys Ala Asn Ser Ser Ser Lys Pro Ser Leu Arg
225 230 235 240
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Pro Gly Tyr Ile
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<210> 508

<211> 248

<212> PRT

<213> Human

<400> 508

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20 25 30 Val Gly Pro Ala Arg Pro Ser Leu Leu Val Pro Pro Pro Pro Arg Pro 35 40 45 Arg Arg Leu Asp Leu Ala Arg Thr Leu Pro Ala Glu Arg Thr Asp Ser 50 60 Gln Ser Leu Tyr Ile Val Tyr Ile Ala Leu Pro Gly Arg Thr Pro Arg 65 70 75 80 Pro Ala Leu Ala Phe Ala Phe Leu Met Pro Ala Cys Cys Asn Arg Pro 85 90 95 Ser Pro Arg Pro Ser Pro Ala His Leu Thr Ala Ser Ser Val Leu Arg Arg Gln Arg His Val Leu Ala Ala Ser Ala Ala Ser Pro Cys Gln Trp
115 120 125 Ser Gly Leu Arg Val Ala His Ser Leu Arg Gln Val Val Ser Leu Cys 130 135 140 Pro Arg Cys Thr Gly Ser Cys Pro Phe Ser Gly Ala Cys Ala Ser Ser 145 150 155 160 Leu Pro Ser Pro Leu Ser Cys Pro His Ser His Ser Gly Ser Trp Gly
165 170 175 Thr Trp Ser Gln Gly Arg Pro Cys Ser Ser Thr Glu Val Ala Gly Leu 180 185 190 Ala Leu Trp Pro Thr Asp Phe Leu Ser Cys Leu Leu Asp Ala Ser Glu

200

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Leu Gln Thr Gln Gly Ser His Gly Phe Ser Phe Thr Pro Thr Gly Phe
                215
                                               220
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Ser Ser Asn Arg Lys Val Gly Val Gly Ser Cys Arg Asp Gly Ala Gly
225 230 235 240
                                              235
Arg Gly Ala Met Gly Gly Leu Phe
                  245
       <210> 509
       <211> 698
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       <213> Mouse
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Val Val Val Ser Leu Glu Arg Leu Met Glu Pro Gln Asp Thr Ala Arg
          20
                                  25
Cys Ser Leu Gly Leu Ser Cys His Leu Trp Asp Gly Asp Val Leu Cys 35 40 45
Leu Pro Glý Ser Leu Gln Ser Ala Pro Gly Pro Val Leu Val Pro Thr 50 60
Arg Leu Gln Thr Glu Leu Val Leu Arg Cys Pro Gln Lys Thr Asp Cys 65 70 75 80
Ala Leu Cys Val Arg Val Val Val His Leu Ala Val His Gly His Trp
85 90 95
Ala Glu Pro Glu Glu Ala Gly Lys Ser Asp Ser Glu Leu Gln Glu Ser
100 105 110
Arg Asn Ala Ser Leu Gln Ala Gln Val Val Leu Ser Phe Gln Ala Tyr
115 120 125
Pro Ile Ala Arg Cys Ala Leu Leu Glu Val Gln Val Pro Ala Asp Leu
130 135 140
Val Gln Pro Gly Gln Ser Val Gly Ser Ala Val Phe Asp Cys Phe Glu
145 150 155 160
Ala Ser Leu Gly Ala Glu Val Gln Ile Trp Ser Tyr Thr Lys Pro Arg
165 170 175
Tyr Gln Lys Glu Leu Asn Leu Thr Gln Gln Leu Pro Asp Cys Arg Gly
180 185 190
Leu Glu Val Arg Asp Ser Ile Gln Ser Cys Trp Val Leu Pro Trp Leu
195 200 205
Asn Val Ser Thr Asp Gly Asp Asn Val Leu Leu Thr Leu Asp Val Ser 210 215 220 . . .
Glu Glu Gln Asp Phe Ser Phe Leu Leu Tyr Leu Arg Pro Val Pro Asp 225 230 235 240
Ala Leu Lys Ser Leu Trp Tyr Lys Asn Leu Thr Gly Pro Gln Asn Ile 245 \phantom{\bigg|} . \phantom{\bigg|} 250 \phantom{\bigg|}
Thr Leu Asn His Thr Asp Leu Val Pro Cys Leu Cys Ile Gln Val Trp 260 265 270
Ser Leu Glu Pro Asp Ser Glu Arg Val Glu Phe Cys Pro Phe Arg Glu
275 280 285
Asp Pro Gly Ala His Arg Asn Leu Trp His Ile Ala Arg Leu Arg Val
290 295 300
Leu Ser Pro Gly Val Trp Gln Leu Asp Ala Pro Cys Cys Leu Pro Gly 305 310 315 320
Lys Val Thr Leu Cys Trp Gln Ala Pro Asp Gln Ser Pro Cys Gln Pro
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Leu Val Pro Pro Val Pro Gln Lys Asn Ala Thr Val Asn Glu Pro Gln
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Thr Trp Glu Lys Val Gln Leu Gln Ala Cys Leu Trp Ala Asp Ser Leu
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Gly Pro Phe Lys Asp Asp Met Leu Leu Val Glu Met Lys Thr Gly Leu
385 390 395 400
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Asn Asn Thr Ser Val Cys Alà Leu Glu Pro Ser Gly Cys Thr Pro Leu
405 410 415
                405
                                      410
Pro Ser Met Ala Ser Thr Arg Ala Ala Arg Leu Gly Glu Glu Leu Leu
            420
                               425
                                                      430
Gln Asp Phe Arg Ser His Gln Cys Met Gln Leu Trp Asn Asp Asp Asn
435 440 445
                                                   445 .
Met Gly Ser Leu Trp Ala Cys Pro Met Asp Lys Tyr Ile His Arg Arg
450 455 460
Trp Val Leu Val Trp Leu Ala Cys Leu Leu Leu Ala Ala Leu Phe 465 470 475 480
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Phe Phe Leu Leu Lys Lys Asp Arg Arg Lys Ala Ala Arg Gly Ser
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                                      490
Arg Thr Ala Leu Leu His Ser Ala Asp Gly Ala Gly Tyr Glu Arg 500 505 510
Leu Val Gly Ala Leu Ala Ser Ala Leu Ser Gln Met Pro Leu Arg Val 515 520 525
Ala Val Asp Leu Trp Ser Arg Arg Glu Leu Ser Ala His Gly Ala Leu 530 535 540
Ala Trp Phe His His Gln Arg Arg IIe Leu Gln Glu Gly Gly Val 545 550 555 560
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Val Ile Leu Leu Phe Ser Pro Ala Ala Val Ala Gln Cys Gln Gln Trp
565 570 575
                                     570
Leu Gln Leu Gln Thr Val Glu Pro Gly Pro His Asp Ala Leu Ala Ala
580 585 590
Trp Leu Ser Cys Val Leu Pro Asp Phe Leu Gln Gly Arg Ala Thr Gly 595 600 605
Arg Tyr Val Gly Val Tyr Phe Asp Gly Leu Leu His Pro Asp Ser Val 610 615 620
Pro Ser Pro Phe Arg Val Ala Pro Leu Phe Ser Leu Pro Ser Gln Leu 625 630 635 640
                                         635
Pro Ala Phe Leu Asp Ala Leu Gln Gly Gly Cys Ser Thr Ser Ala Gly 645 650 655
                                     650
Arg Pro Ala Asp Arg Val Glu Arg Val Thr Gln Ala Leu Arg Ser Ala
660 665 670
Leu Asp Ser Cys Thr Ser Thr Ser Glu Ala Pro Gly Cys Cys Glu Glu
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Trp Asp Leu Gly Pro Cys Thr Thr Leu Glu
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<211> 1700

<212> DNA

<213> Rat

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tggtagcccg tccacgtcca cgagtagact tcggagagga cctgcaagtg cctgaagcag
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aaaaaaaaa aaaaaaaaa
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Leu Ala Pro Gly Leu Gln His Phe Gly Cys Ser Ile His Gly Gln Leu
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465 470 475 480
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Thr Val Lys Tyr Leu Tyr Leu Leu Phe His Pro Asn Asn Phe Ile His 435 440 445
 Asn Asn Gly Ser Thr Phe Asp Ser Val Met Thr Pro His Gly Glu Cys
450 455 460
 Ile Leu Gly Ala Gly Gly Tyr Ile Phe Asn Thr Glu Ala His Pro Ile
465 470 475 480
 Asp Pro Ala Ala Leu His Cys Cys Arg Arg Leu Lys Glu Glu Gln Trp 485 490 495
 Glu Val Glu Asp Leu Ile Lys Glu Phe Tyr Ser Leu Arg Gln Ser Arg
500 505 510
 Ser Arg Ala Gln Arg Lys Thr Val Ser Ser Gly Pro Trp Glu Pro Pro 515 520 525
 Ala Gly Pro Gly Thr Leu Ser Ser Pro Glu Asn Gln Pro Arg Glu Lys 530 540
 Gln Pro Ala Arg Gln Arg Ala Pro Leu Leu Ser Cys Pro Ser Gln Pro 545 550 550 555 560
 Phe Thr Ser Lys Leu Ala Leu Leu Gly Gln Val Phe Leu Asp Ser Ser
                    565
                                            570
 <210> 627
 <211> 226
 <212> PRT
 <213> Rat
 <400> 627
Arg Lys Ile Lys Asn Lys Ile Ser Ala Gln Glu Ser Arg Lys Lys 1 5 10 15
                                         10
Lys Glu Tyr Val Glu Cys Leu Glu Lys Lys Val Glu Thr Tyr Thr Ser 20 25 30 .
Glu Asn Asn Glu Leu Trp Lys Lys Val Glu Thr Leu Glu Thr Ala Asn 35 40 45
Arg Thr Leu Leu Gln Gln Leu Gln Lys Leu Gln Thr Leu Val Thr Ser 50 55 60
Lys Ile Ser Arg Pro Tyr Lys Met Ala Ala Thr Gln Thr Gly Thr Cys 65 70 75 80
Leu Met Val Ala Ala Leu Cys Phe Val Leu Val Leu Gly Ser Leu Ala
85 90 95
Pro Cys Leu Pro Ala Phe Ser Ser Gly Ser Lys Thr Val Lys Glu Asp
100 105 110
Pro Val Ala Ala Asp Ser Val Tyr Ala Ala Ser Gln Met Pro Ser Arg
Ser Leu Leu Phe Tyr Asp Asp Gly Ala Gly Ser Trp Glu Asp Gly His
130 135 140
Arg Gly Ala Leu Leu Pro Val Glu Pro Pro Glu Gly Trp Glu Leu Lys
145 150 155 160
Pro Gly Gly Pro Ala Glu Pro Arg Pro Gln Asp His Leu Arg His Asp 165 170 . . . 175
His Ala Asp Ser Ile His Glu Thr Thr Lys Tyr Leu Arg Glu Thr Trp 180 190
Pro Glu Asp Thr Glu Asp Asn Gly Ala Ser Pro Asn Phe Ser His Pro
195 200 205
Lys Glu Trp Phe His Asp Arg Asp Leu Gly Pro Asn Thr Thr Ile Lys 210 215 220.
Leu Ser
225
```

<210> 628

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<211> 82
<212> PRT
 <213> Rat
<400> 628
Pro Ile Thr Leu Ser Cys Gln Ser Gly Asn Ala Ala Ser Leu Gln Pro
Leu His Phe Pro Pro Val Pro Pro Glu Ala Cys Pro Cys Ala Phe Arg
                                  25
Leu Arg Pro Phe Cys Leu His Thr Gly Cys Ala Gly Cys Ser Leu Arg
35 40 45
                                                   45
Ala Ala Thr Glu Gln Cys Ala Val Ala Leu Ala Pro Gln Leu Pro Ser
50 55 60
Ala Ser Arg Ala Phe Pro Pro Leu Thr Leu Cys Asn Pro Cys Val Leu
Thr Arg
<210> 629
<211> 242
<212> PRT
<213> Rat
<400> 629
Met Ala Gly Ala Gly Pro Val Leu Ser Ile Leu Gly Leu Leu Val
                                      10
Ser Ala Leu Phe Gly Val Leu Gly Glu Arg Pro Asn Pro Asp Leu Gly
            20
                                  25
Ala His Pro Glu Arg Arg Ser Gln Val Gly Pro Gly Ala Thr Glu Pro 35 40 45
Arg Arg Gln Pro Pro Pro Lys Asp Gln Arg Glu Arg Ala Arg Ala Gly 50 55 60
Ser Leu Ser Leu Gly Ala Leu Tyr Thr Ala Ala Ile Val Ala Phe Val 65 70 75 80
Leu Phe Lys Cys Leu Gln Gln Gly Pro Asp Glu Ala Ala Val Pro Arg
85 90 95
Glu Glu Lys Asn Lys Lys Lys Ser Ser Gln Ser Glu Gln Gln Leu Val
100 105 110
Gln Leu Thr Gln Gln Leu Ala Gln Thr Glu Glu His Leu Asn Asn Leu
115 120 125
Met Thr Gln Leu Asp Pro Leu Phe Glu Arg Val Thr Thr Leu Val Gly
   130
               135
Thr Gln Arg Glu Leu Leu Asn Ala Lys Leu Lys Thr Ile His His Leu 145 150 155 160
Leu Gln Asp Cys Lys Pro Gly Ile Gly Val Glu Ala Pro Glu Pro Glu
165 170 175
Ala Pro Ile His Phe Pro Glu Asp Leu Gly Lys Glu Asp. Gln Glu Asp
180 185 190
Ala Gly Asn Ser Gln Ala Trp Glu Glu Pro Ile Asn Trp Ser Ser Glu
195 200 205
Thr Trp Asn Leu Ala Pro Ser Trp Glu Val Glu Gln Gly Leu Arg Arg
                        215
                                              220
Arg Trp His Lys Thr Lys Gly Pro Ala Val Asn Gly Gly Gln Ala Leu
225
                     230
                                           235
Lys Val
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<210> 630
<211> 289
<212> PRT
<213> Rat
<400> 630
Met Ile Val Leu Leu Tyr Val Thr Ser Leu Ala Ile Cys Ala Ser Gly
                                       10
Gln Pro Arg Gly Asn Gln Ala Lys Gly Glu Ser Tyr Ser Pro Arg Tyr
20 25 30
Ile Cys Ser Ile Pro Gly Leu Pro Gly Pro Pro Gly Pro Pro Gly Ala 35 40 45
Asn Gly Ser Pro Gly Pro His Gly Arg Ile Gly Leu Pro Gly Arg Asp 50 55 60
Gly Arg Asp Gly Arg Lys Gly Glu Lys Gly Glu Lys Gly Thr Ala Gly 65 70 75 80
Leu Lys Gly Lys Thr Gly Pro Leu Gly Leu Ala Gly Glu Lys Gly Asp
85 90 95
Gln Gly Glu Thr Gly Lys Lys Gly Pro Ile Gly Pro Glu Gly Glu Lys
100 105 110
Gly Glu Val Gly Pro Ala Gly Pro Pro Gly Pro Lys Gly Asp Arg Gly 115 120 125
Asp Gln Gly Asp Pro Gly Leu Pro Gly Val Cys Arg Cys Gly Ser Ile
130 135 140
Val Leu Lys Ser Ala Phe Ser Val Gly Ile Thr Thr Ser Tyr Pro Glu
145 150 155 160
Glu Arg Leu Pro Ile Ile Phe Asn Lys Val Leu Phe Asn Glu Gly Glu 165 170 175
His Tyr Asn Pro Ala Thr Gly Lys Phe Ile Cys Ala Phe Pro Gly Ile
180 185 190
Tyr Tyr Phe Ser Tyr Asp Ile Thr Leu Ala Asn Lys His Leu Ala Ile
Gly Leu Val His Asn Gly Gln Tyr Arg Ile Arg Thr Phe Asp Ala Asn 210 215 220
Thr Gly Asn His Asp Val Ala Ser Gly Ser Thr Val Ile Tyr Leu Gln 225 230 235 240
Pro Glu Asp Glu Val Trp Leu Glu Ile Phe Phe Asn Asp Gln Asn Gly
245 250 255
Leu Phe Ser Asp Pro Gly Trp Ala Asp Ser Leu Phe Ser Gly Phe Leu 260 265 270
            260
                                 265 270
Leu Tyr Val Asp Thr Asp Tyr Leu Asp Ser Ile Ser Glu Asp Asp Glu
                               280
                                                     285
Leu
<210> 631
<211> 213
<212> PRT
<213> Rat
Met Val Leu Gly Gly Cys Pro Val Ser Tyr Leu Leu Leu Cys Gly Gln 1 5 15
Ala Ala Leu Leu Gly Asn Leu Leu Leu Leu His Cys Val Ser Arg 20 25 30
Ser His Ser Phe Asn Ala Thr Ala Glu Leu Asp Leu Thr Pro Ser Gly
                               40
```

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Ala Ala His Leu Glu Gly Pro Ala Ala Ser Ser Trp Glu Tyr Ser Asp
Pro Asn Ser Pro Val Ile Leu Cys Ser Tyr Leu Pro Asp Glu Phe Val
                     70
                                          75
Asp Cys Asp Ala Pro Val Asp His Val Gly Asn Ala Thr Ala Tyr Gln
               85
                                    90
Glu Leu Gly Tyr Gly Cys Leu Lys Phe Gly Gly Gln Ala Tyr Ser Asp
100 105 110
Val Glu His Thr Ala Val Gln Cys Arg Ala Leu Glu Gly Ile Glu Cys
115 120 125
Ala Ser Pro Arg Thr Phe Leu Arg Lys Asn Lys Pro Cys Ile Lys Tyr
130 135 140
Thr Gly His Tyr Phe Ile Thr Thr Leu Leu Tyr Ser Phe Phe Leu Gly 145 150 155 160
Cys Phe Gly Val Asp Arg Phe Cys Leu Gly His Thr Gly Thr Ala Val
165 170 175
Gly Lys Leu Leu Thr Leu Gly Gly Leu Gly Ile Trp Trp Phe Val Asp
          180
                                185
                                                  190
Leu Ile Leu Leu Ile Thr Gly Gly Leu Met Pro Ser Asp Gly Ser Asn
    195
                             200
Trp Cys Thr Val Tyr
   210
<210> 632
<211> 167
<212> PRT
<213> Rat
<400> 632
Met Ala Ser Pro Arg Thr Ile Thr Ile Val Ala Leu Ser Val Ala Leu
                                     10
Gly Leu Phe Phe Val Phe Met Gly Thr Ile Lys Leu Thr Pro Arg Leu
20 25 30
Ser Lys Asp Ala Tyr Ser Glu Met Lys Arg Ala Tyr Lys Ser Tyr Val
35 40 45
Arg Ala Leu Pro Leu Leu Lys Lys Met Gly Ile Asn Ser Ile Leu Leu 50 60
Arg Lys Ser Ile Gly Ala Leu Glu Val Ala Cys Gly Ile Val Met Thr 65 70 75 80
Leu Val Pro Gly Arg Pro Lys Asp Val Ala Asn Phe Phe Leu Leu Leu 65 90 95
Leu Val Leu Ala Val Leu Phe Phe His Gln Leu Val Gly Asp Pro Leu
100 105 110
Lys Arg Tyr Ala His Ala Leu Val Phe Gly Ile Leu Thr Cys Arg
115 120 125
Leu Leu Ile Ala arg Lys Pro Glu Asp Arg Ser Phe Glu Lys Lys Ala
130 135 140 -
Leu Pro Glu Ser Ala Glu Glu Gln Pro Ser Leu Tyr Glu Lys Ala Pro
145 150
                                        155
Gln Gly Lys Val Lys Val Ser
                165
<210> 633
<211> 138
<212> PRT
<213> Rat
```

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<400> 633
. Phe Ile Arg Gly Met Leu Lys Leu Ile Leu Leu Leu Phe Ser Gly
                 5
                                   10 ·
 Ala Thr Leu Ser Ser Thr Trp Phe Thr Leu Thr Cys Leu Asn Ser Val
      20
                               25
 Thr His Leu Pro Leu Thr Thr Val Thr Leu Tyr Ala Ser Cys Ile Leu
        35
                             40
 Leu Gly Val Phe Leu Asn Ser' Ser Val Pro IIe Phe Phe Glu Leu Phe
     50
                       55
                                            60
 Val Glu Thr Val Tyr Pro Val Pro Glu Gly Ile Thr Cys Gly Val Val
65 70 75 80
 Thr Phe Leu Ser Asn Met Phe Met Gly Val Leu Leu Phe Phe Val Thr
               85
                                   90
 Phe Tyr His Thr Glu Leu Ser Trp Phe Asn Trp Cys Leu Pro Gly Ser
 Cys Leu Leu Ser Leu Leu Leu Ile Leu Cys Phe Arg Glu Ser Tyr Asp
115 120 125
                                                125
 Arg Leu Tyr Leu Asp Val Val Ser Val
    130
                         135
 <210> 634
 <211> 75
 <212> PRT
 <213> Rat
Met Ile Gly Asp Ile Leu Leu Phe Gly Thr Leu Leu Met Asn Ala Gly 1 5 10 15
Ala Val Leu Asn Phe Lys Leu Lys Lys Lys Asp Thr Gln Gly Phe Gly 20 25 30
                                25
                                                   30
 Glu Glu Ser Arg Glu Pro Ser Thr Gly Asp Asn Ile Arg Glu Phe Leu
       35
                                               45
Leu Ser Leu Arg Tyr Phe Arg Ile Phe Ile Ala Leu Trp Asn Val Phe 50 55 60
 Met Met Leu Cys Met Ile Val Leu Phe Gly Ser
 65
                     70
 <210> 635
 <211> 186
 <212> PRT
 <213> Rat
 <400> 635
 Met Val Ala Ala Val Ala Thr Ala Trp Leu Leu Trp Ala Ala Ala
                                    10
Cys Thr Gln Ser Glu Gln Asp Phe Tyr Asp Phe Lys Ala Val Asn Ile
20 25 .30
 Arg Gly Lys Leu Val Ser Leu Glu Lys Tyr Arg Gly Ser Val Ser Leu
       35
                            40
 Val Val Asn Val Ala Ser Glu Cys Gly Phe Thr Asp Gln Asn Tyr Arg
                      55
                                         60
Ala Leu Gln Gln Leu Gln Arg Asp Leu Gly Pro Tyr His Phe Asn Val 65 70 75 . . 80
                   70
Leu Ala Phe Pro Cys Asn Gln Phe Gly Gln Gln Glu Pro Asp Ser Asn
                85
                                    90
Arg Glu Ile Glu Asn Phe Ala Arg Arg Thr Tyr Ser Val Ser Phe Pro
            100
```

105,

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Met Phe Ser Lys Ile Ala Val Thr Gly Thr Gly Ala His Pro Ala Phe
        115
                             120
                                                   125
Lys Tyr Leu Thr Gln Thr Ser Gly Lys Glu Pro Thr Trp Asn Phe Trp
    130
                        135
                                               140
Lys Tyr Leu Val Ala Pro Asp Gly Lys Val Val Gly Ala Trp Asp Pro
145
         150 155
Thr Val Pro Val Glu Glu Ile Lys Pro Arg Ile Thr Glu Gln Val Met
165 170 175
Lys Leu Ile Leu Gln Lys Arg Glu Asp Leu
            180
                                  185
<210> 636
<211> 930
<212> PRT
<213> Rat
<400> 636
Met Pro Ser Leu Leu Ser Leu Val Leu Thr Phe Leu Ala Val Ser Ser 1 10 15
Pro Ser Cys Cys Gln Asn Ser Asp Thr Ala Ser Pro Lys Ala Ser Asn
20 25 30
Gly Ala Ser Phe Leu Trp Asn Asn Met Arg Leu Pro Glu Tyr Ile Thr
       35
                           40
Pro Ile His Tyr Asp Leu Met Ile His Ala Asn Leu Ser Thr Leu Thr 50 55 60
Phe Trp Gly Lys Thr Glu Val Glu Ile Thr Val Ser Gln Pro Thr Ser
                    70
                                         75
Thr Ile Ile Met His Ser His Gln Leu Gln Ile Ser Lys Ala Thr Leu
85 90 95
Arg Arg Gly Ala Glu Glu Met Leu Pro Glu Glu Pro Leu Lys Leu Met 100 105 110
Glu Tyr Ser Ala His Glu Gln Val Ala Leu Leu Thr Ala Gln Pro Leu
115 120 125
Leu Ala Gly Ser Val Tyr Thr Val Ile Ile Thr Tyr Ala Ala Asn Leu
   130
                       135 140
Ser Glu Asn Phe His Gly Phe Tyr Lys Ser Thr Tyr Arg Thr Glu Glu 145 150 150 155 160
Gly Glu Arg Arg Ile Leu Ala Ala Thr Gln Phe Glu Pro Thr Ala Ala
165 170 175
Arg Met Ala Phe Pro Cys Phe Asp Glu Pro Ala Leu Lys Ala Ser Phe 180 185 190
Ser Ile Lys Ile Lys Arg Asp Pro Arg His Leu Ala Ile Ser Asn Met 195 200 205
Pro Leu Val Lys Ser Val Thr Val Ala Glu Gly Leu Ile Glu Asp His 210 215 220
Phe Asp Ile Thr Val Lys Met Ser Thr Tyr Leu Val Ala Phe Ile Ile 225 230 230 240
Ser Asp Phe Lys Ser Val Ser Lys Met Thr Lys Ser Gly Val Lys Val 245 250 255
Ser Val Tyr Ala Val Pro Asp Lys Ile Asn Gln Ala Asp Tyr Ala Leu
260 265 270
Asp Ala Ala Val Thr Leu Leu Glu Phe Tyr Glu Asp Tyr Phe Ser Ile
275 280 285
Pro Tyr Pro Leu Pro Lys Gln Asp Leu Ala Ala Ile Pro Asp Phe Gln 290 295 300
Ser Gly Ala Met Glu Asn Trp Gly Leu Thr Thr Tyr Arg Glu Ser Ala
                     310
                                          315
```

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Leu Leu Tyr Asp Lys Glu Lys Ser Ser Ala Ser Ser Lys Leu Gly Ile
                   325
                                         330 -
 Thr Met Thr Val Ser His Glu Leu Ala His Gln Trp Phe Gly Asn Leu 340 345 350
 Val Thr Met Glu Trp Trp Asn Asp Leu Trp Leu Asn Glu Gly Phe Ala
355 360 365
Lys Phe Met Glu Phe Val Ser Val Thr Val Thr His Pro Glu Leu Lys 370 380
Val Glu Glu Tyr Phe Phe Gly Lys Cys Val Asn Ala Met Glu Val Asp
385 390 395 400
Ala Leu Asn Ser Ser His Pro Val Ser Thr Pro Val Glu Asn Pro Ala
405 410 415
Glin Ile Arg Glu Met Phe Asp Glu Val Ser Tyr Glu Lys Gly Ala Cys
420 425 430
Ile Leu Asn Met Leu Arg Asp Tyr Leu Ser Ala Asp Thr Phe Lys Arg
435 440 445
Gly Ile Val Gln Tyr Leu Gln Lys Tyr Ser Tyr Lys Asn Thr Lys Asn
450 455 460
                                                460
Glu Asp Leu Trp Asn Ser Met Met His Ile Cys Pro Thr Asp Gly Thr
465 470 475 480
Gln Thr Met Asp Gly Phe Cys Ser Arg Asn Gln His Ser Ser Ser Thr
485 490 495
Ser His Trp Arg Gln Glu Val Ile Asp Ile Lys Ser Met Met Asn Thr 500 505 510
Trp Thr Leu Gln Lys Gly Phe Pro Leu Ile Thr Ile Thr Val Arg Gly 515 520 525
Arg Asn Val His Leu Lys Gln Glu His Tyr Met Lys Gly Ser Glu Cys
530 535 540
Phe Pro Glu Thr Gly Ser Leu Trp His Val Pro Leu Thr Phe Ile Thr 545 550 555 . 560
Ser Lys Ser Asp Ser Val Gln Arg Phe Leu Leu Lys Thr Lys Thr Asp
565 570 575
Val Ile Ile Leu Pro Glu Ala Val Glu Trp Ile Lys Phe Asn Val Gly 580 590
Met Asn Gly Tyr Tyr Ile Val His Tyr Gly Asp Asp Gly Trp Ala Ser
595 600 605
Leu Asn Gly Leu Leu Lys Glu Ala His Thr Thr Ile Ser Ser Asn Asp
 · 610
                         615
                                                620
Arg Ala Ser Leu Ile Asn Asn Ala Phe Gln Leu Val Ser Ile Gly Lys 625 630 635
                                           635
                   630
Leu Ser Ile Glu Lys Ala Leu Asp Leu Ile Leu Tyr Leu Lys Asn Glu 645 650 655
Thr Glu Ile Met Pro Ile Phe Gln Gly Leu Asn Glu Leu Ile Pro Met 660 665 670
Tyr Lys Leu Met Glu Lys Arg Asp Met Val Glu Val Glu Thr Gln Phe
675 680 685
                                                   685
Lys Asp Phe Leu Leu Arg Leu Leu Lys Asp Leu Ile Asn Lys Gln Thr 690 695 700
Trp Thr Asp Glu Gly Ser Val Ser Glu Arg Met Leu Arg Ser Gln Leu 705 710 715 720
Leu Leu Leu Ala Cys Val His Arg Tyr Gln Leu Cys Val Gln Arg Ala 725 730 735
Glu Arg Tyr Phe Arg Glu Trp Lys Ala Ser Asn Gly Asn Met Ser Leu
740 745 750
Pro Ile Asp Val Thr Leu Ala Val Phe Ala Val Gly Ala Gln Asn Thr
755 760 765
Glu Gly Trp Asp Phe Leu Tyr Ser Lys Tyr Gln Ser Ser Leu Ser Ser
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770
                          775
Thr Glu Lys Ser Gln Ile Glu Phe Ser Leu Cys Ile Ser Gln Asp Pro 785 790 795 800
Glu Lys Leu Gln Trp Leu Leu Asp Gln Ser Phe Lys Gly Glu Ile Ile
805 810 815
Lys Thr Gln Glu Phe Pro His Ile Leu Thr Leu Ile Gly Arg Asn Pro 820 825 830
Val Gly Tyr Pro Leu Ala Trp Lys Phe Leu Lys Glu Asn Trp Asn Lys
835 840 845
                                                   845
Ile Val Gln Lys Phe Glu Leu Gly Ser Ser Ser Ile Ala His Met Val
850 855 860
Met Gly Thr Thr Asn Gln Phe Ser Thr Arg Ala Arg Leu Glu Glu Val
865 870 875 880
                                                                 880
Lys Gly Phe Phe Ser Ser Leu Lys Lys Asn Gly Ser Gln Leu Arg Cys
885 890 895
Val Gln Gln Thr Ile Glu Thr Ile Glu Glu Asn Ile Arg Trp Met Asp
900 905 910
Lys Asn Phe Asp Lys Ile Arg Leu Trp Leu Gln Lys Glu Arg Gln Glu
       915
                              920
Leu Leu
   930
<210> 637
<211> 161
<212> PRT
<213> Rat
<400> 637
Met Ala Tyr His Ser Gly Tyr Gly Val His Ala Met Ala Phe Ile Thr
                 5
                                      10
Tyr Val Leu Leu Ala Gly Met Ala Leu Gly Ile Gln Gln Arg Phe Ser 20 25 30
Pro Glu Val Leu Gly Leu Cys Ala Ser Thr Ala Leu Val Trp Val Leu
35 40 45
Met Glu Val Leu Ala Leu Leu Leu Gly Leu Tyr Leu Ala Thr Val Arg
Ser Glu Leu Gly Thr Phe His Leu Leu Ala Tyr Ser Gly Tyr Lys Tyr 65 70 75 80
Val Gly Met Ile Leu Ser Val Leu Thr Gly Leu Leu Phe Gly Ser Asp
85 90 95
                                     90
Gly Tyr Tyr Val Ala Leu Ala Trp Thr Ser Ser Ala Leu Met Tyr Phe 100 105 110
Thr Val Arg Ser Leu Arg Thr Ala Ala Ser Gly Pro Asp Ser Met Gly 115 120 125
Gly Pro Thr Pro Arg Gln His Leu Gln Leu Tyr Leu Thr Leu Gly Ala
                       135
Ala Ala Phe Gln Pro Leu Ile Ile Tyr Trp Leu Thr Phe His Leu Val
145
                     150
                                            155
Arg
<210> 638
<211> 165
<212> PRT
<213> Rat
<400> 638
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Met Ala Arg Ala Ala Gly Ile Thr Ala Ala Ile Thr Leu Ala Leu Leu
                                   10
Gly Val Leu Ala Leu Gly Ala Gly Asp Gly Asp Phe Arg Leu Asp Asp
                              25
           20
Ala Leu Glu Asp Thr Asp Lys Lys Pro Thr Pro Lys Pro Pro Thr Pro
      35
                          40
                                             45
Lys Lys Pro Ser Ser Gly Asp Phe Asp Leu Glu Glu Ala Leu Thr Gly 50 60
Gly Ala Asp Glu Asp Pro Arg Arg Pro Gly Ser Arg Pro Lys Pro Asp
65 70 75 80
                                      75
Pro Lys Pro Pro Gly Pro Pro Arg Asp Ser Gly Gly Ile Ser Asp Arg
              85
                                   90
                                                      95
Asp Leu Glu Asp Val Ala Gly His Gly Gly Arg Gly Gly Gly Ala Gly 100 105 110
Asp Arg Gly Thr Asp Gly Ala Glu Ser Glu Gly Gln Pro Gln Gly Leu
       115
                         120
Ile Pro Gly Val Val Ala Ala Val Leu Ala Ala Leu Ala Gly Ala Val
               135
                                         140
Ser Ser Phe Val Ala Tyr Gln Lys Arg Arg Leu Cys Phe Arg Glu Gly
145
         150
                                       155
Gly Ser Ala Pro Val
               165
<210> 639
<211> 61
<212> PRT
<213> Rat
<400> 639 .
Met His Ile Tyr Lys Tyr Val His Ile Asn Tyr Tyr Leu His Leu His
                                  10
                                                      15
Ile Cys Ile Tyr Val Tyr Thr His Ile Ser Val Gly Met Cys Ile Arg
          20
                              25
Ile Cys Leu Pro Ser Ser Ser His Trp Lys Lys Glu Ser Ile Arg Ser
      35
                           40
Gly Gly Ser Lys Asn Ala His Tyr Pro Gly Ser Gly Ile
                     55
<210> 640
<211> 73
<212> PRT
<213> Rat
<400> 640
Met Cys Phe Ser Leu Cys Ser Val Glu Val Phe Phe Leu Lys Gln Asn
Ser Asn Leu Leu Pro Ala His Ile Phe Ile Arg Ala Ser Pro Ile Cys
20 25 30
Ile Ile Gly Asn Glu Tyr Glu Tyr Ile Phe Met Tyr Val Cys Asn His
      35
                          40
                                             45
Arg Ser His Leu Tyr Leu Gly Phe Ala Ala Ala Asp Tyr Phe Phe Pro
  50 ·
                      55
                                           60 ·
His His Gly Thr Gly Asn Cys Phe Gln
```

<210> 641

<211> 442 <212> PRT <213> Rat <400> 641 Met Pro Val Leu Trp Leu Leu Leu Leu Pro Leu Pro Leu Leu 10 Ala Met Leu Cys Gln Gln Arg Ser Pro Gly Ala Arg Pro Cys Trp Leu Ile Ser Leu Gln His Arg Val Ala Cys Val Val Leu Ser Trp Ala Ala 35 40 45 Ala Trp Gln Arg Arg Lys Leu Glu Gln Ser Thr Leu Asn Val Ser Gln 50 55 60 60 Ser Gln Gln Gln Ala Leu Met Gly Cys Leu Lys Glu Ala Gln Gly Ser 65 70 75 80 Cys Cys Leu Pro Arg Glu Asn Thr Asp Met Thr Thr Phe Arg Asn Leu 85 90 95 Pro Leu Thr Lys Thr Ser His Thr Gln Gln Lys Glu Ser Glu Glu Lys
100 105 110 Leu Leu Pro Pro Thr Leu Pro Gln Tyr His Gly Asp Ala Ser Leu Gln 115 120 125 Val Thr Leu Leu Gly Leu Met Thr Leu Asn Lys Ala Tyr Pro Glu Val 130 140 Leu Ala Pro Gly Ser Thr Ala Cys Val Thr Pro Thr Ser Pro Trp Pro 145 150 . 155 160 Tyr Ser Val Pro Trp Leu Gly His Ala Leu Gly Arg Val Ser Pro Ile 165 170 175 Gly Ala Lys Asp Ala Arg Thr Leu Leu Leu Glu Ala Leu Ile Ser Pro 180 185 190 Gly Leu Arg Val Leu Glu Ala Arg Thr Ala Val Glu Leu Leu Asp Val 195 200 205 . Phe Val Gly Leu Glu Ala Asp Gly Glu Glu Leu Ala Glu Val Ile Ala 210 215 220 Ser Gly Ser Leu Gly Lys Leu Pro Arg Arg Ala Ala Glu Leu Gln Glu 225 230 235 Ala Leu Glu Gln Gly Pro Arg Gly Leu Ala Leu Arg Leu Trp Pro Lys 245 250 255 Leu Gln Val Val Val Thr Leu Asp Ala Gly Gly Gln Ala Glu Ala Val
260 265 270 Ala Ala Leu Arg Val Leu Trp Cys Gln Gly Leu Ala Phe Phe Ser Pro 275 280 285 Ala Tyr Ala Ala Ser Gly Gly Val Met Ala Ile Asn Leu Trp Pro Glu 290 295 300

Gln Pro Gln Gly Ser Tyr Leu Leu Ser Pro Gly Val Pro Phe Ile Glu 305 310 315 320 Leu Leu Pro Ile Lys Glu Gly Thr Gln Glu Glu Ala Ala Ser Thr Leu 325 330 335 Ile Gly Thr Tyr Asn Gln Cys Pro Val Val Arg Phe Thr Cys Arg Leu 370 380 Gly Gln Thr Leu Ser Val Arg Gly Glu Val Thr Asp Glu Asn Val Phe 390 395 Ser Val Ala Leu Ala Gln Ala Val Gly Gln Cys Gln Gly Pro Ser Cys 405 . 410

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Trp Thr Met Ser Val Trp Arg Ala Thr Phe Trp Thr Pro Met Arg Asp
           420
                              425
Pro Pro His Thr Thr Lys Cys Leu Trp Ser
                            440
        435
<210> 642
<211> 65
<212> PRT
<213> Rat
<400> 642
Met Thr Val Cys Thr Leu Leu Val Ala Lys Ser Thr Leu Leu Leu Ser
               5
                                  10
                                                        15
Leu Ser Cys Leu Leu Leu Cys Ser Leu Fhe Leu Tyr Ser Val Ser Gly 20 25 30.
Ser Tyr Ser Arg Cys Pro Val Arg Trp Leu Val Cys Leu Ser Ser Gln 35 40 45
                         40
                                               45
Leu Pro Trp Ala Thr Ser Gln Ser Leu Leu Lys Arg Lys Leu Ser Met
                       55
                                            60
Asn
65
<210> 643
<211> 197
<212> PRT
<213> Rat
<400> 643
Pro Arg Pro Gly Arg Ala Arg Thr Leu Arg Ser Pro Ser Gly Ser Arg
                                   10
Val Val Gln Arg Pro Arg Asn Asp Gly Val Ala Ala Leu Thr Gly Ala
20 25 30
Gly Gly Cys Arg Ala Pro Arg Ala Gly Met Ala Gly Gln Phe Arg Ser 35 40 45
Tyr Val Trp Asp Pro Leu Leu Ile Leu Ser Gln Ile Val Leu Met Gln 50 55 60
Thr Val Tyr Tyr Gly Ser Leu Gly Leu Trp Leu Ala Leu Val Asp Ala 65 70 75 80
Leu Val Arg Ser Asn Pro Ser Leu Asp Gln Met Phe Asp Ala Glu Ile
                        90
             85
                                                       95
Leu Gly Phe Ser Thr Pro Pro Gly Arg Leu Ser Met Met Ser Phe Val
Leu Asn Ala Leu Thr Cys Ala Leu Gly Leu Leu Tyr Phe Ile Arg Arg
115 120 125
Gly Lys Gln Cys Leu Asp Phe Thr Val Thr Val His Phe Phe His Leu
130 135 140
Leu Gly Cys Trp Leu Tyr Ser Ser Arg Phe Pro Ser Ala Leu Thr Trp 145 150 150 160
Trp Leu Val Gln Ala Val Cys Ile Ala Leu Met Ala Val Ile Gly Glu
165 170 175
Tyr Leu Cys Met Arg Thr Glu Leu Lys Glu Ile Pro Leu Ser Ser Ala
          180
                       185
                                     190
Pro Lys Ser Asn Val
       195
<210> 644
<211> 930
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<212> PRT <213> Rat

<400> 644 Met Pro Ser Leu Leu Ser Leu Val Leu Thr Phe Leu Ala Val Ser Ser 5 10 Pro Ser Cys Cys Gln Asn Ser Asp Thr Ala Ser Pro Lys Ala Ser Asn 20 25 30 25 30 Gly Ala Ser Phe Leu Trp Asn Asn Met Arg Leu Pro Glu Tyr Ile Thr 35 40 45 40 45 Pro Ile His Tyr Asp Leu Met Ile His Ala Asn Leu Ser Thr Leu Thr 55 Phe Trp Gly Lys Thr Glu Val Glu Ile Thr Val Ser Gln Pro Thr Ser 65 70 75 80 Thr Ile Ile Met His Ser His Gln Leu Gln Ile Ser Lys Ala Thr Leu 85 90 95 Arg Arg Gly Ala Glu Glu Met Leu Pro Glu Glu Pro Leu Lys Leu Met 100 105 110 Glu Tyr Ser Ala His Glu Gln Val Ala Leu Leu Thr Ala Gln Pro Leu 115 120 125 Leu Ala Gly Ser Val Tyr Thr Val Ile Ile Thr Tyr Ala Ala Asn Leu 130 135 140 Ser Glu Asn Phe His Gly Phe Tyr Lys Ser Thr Tyr Arg Thr Glu Glu 145 150 155 160 Gly Glu Arg Arg Ile Leu Ala Ala Thr Gln Phe Glu Pro Thr Ala Ala 165 170 175 Arg Met Ala Phe Pro Cys Phe Asp Glu Pro Ala Leu Lys Ala Ser Phe 180 185 190 Ser Ile Lys Ile Lys Arg Asp Pro Arg His Leu Ala Ile Ser Asn Met 195 200 205 200 205 Pro Leu Val Lys Ser Val Thr Val Ala Glu Gly Leu Ile Glu Asp His . 215 220 Phe Asp Ile Thr Val Lys Met Ser Thr Tyr Leu Val Ala Phe Ile Ile 225 230 240 Ser Asp Phe Lys Ser Val Ser Lys Met Thr Lys Ser Gly Val Lys Val . 245 250 255 Ser Val Tyr Ala Val Pro Asp Lys Ile Asn Gln Ala Asp Tyr Ala Leu 260 265 270 Asp Ala Ala Val Thr Leu Leu Glu Phe Tyr Glu Asp Tyr Phe Ser Ile 275 280 285 Pro Tyr Pro Leu Pro Lys Gln Asp Leu Ala Ala Ile Pro Asp Phe Gln 290 295 300 295 300 Ser Gly Ala Met Glu Asn Trp Gly Leu Thr Thr Tyr Arg Glu Ser Ala 305 310 315 320 Leu Leu Tyr Asp Lys Glu Lys Ser Ser Ala Ser Ser Lys Leu Gly Ile 325 330 335 , Thr Met Thr Val Ser His Glu Leu Ala His Gln Trp Phe Gly Asn Leu 340 345 350 Val Thr Met Glu Trp Trp Asn Asp Leu Trp Leu Asn Glu Gly Phe Ala 355 360 365 Lys Phe Met Glu Phe Val Ser Val Thr Val Thr His Pro Glu Leu Lys 370 375 380 Val Glu Glu Tyr Phe Phe Gly Lys Cys Phe Asn Ala Met Glu Val Asp 385 390 395 400 Ala Leu Asn Ser Ser His Pro Val Ser Thr Pro Val Glu Asn Pro Ala 405 410 Gln Ile Arg Glu Met Phe Asp Glu Val Ser Tyr Glu Lys Gly Ala Cys

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425
Ile Leu Asn Met Leu Arg Asp Tyr Leu Ser Ala Asp Thr Phe Lys Arg
435 440 445
Glu Asp Leu Trp Asn Ser Met Met His Ile Cys Pro Thr Asp Gly Thr
465 470 475 480
Gln Thr Met Asp Gly Phe Cys Ser Arg Asn Gln His Ser Ser Ser Thr
485 490 495
                                      490
Ser His Trp Arg Gln Glu Val Ile Asp Ile Lys Ser Met Met Asn Thr 500 505 510
Trp Thr Leu Gln Lys Gly Phe Pro Leu Ile Thr Ile Thr Val Arg Gly 515 520 525
Arg Asn Val His Leu Lys Gln Glu His Tyr Met Lys Gly Ser Glu Cys 530 540
Phe Pro Glu Thr Gly Ser Leu Trp His Val Pro Leu Thr Phe Ile Thr 545 550 550 555
Ser Lys Ser Asp Ser Val Gln Arg Phe Leu Leu Lys Thr Lys Thr Asp 565 570 575
Val Ile Ile Leu Pro Glu Ala Val Glu Trp Ile Lys Phe Asn Val Gly 580 585 590
Met Asn Gly Tyr Tyr Ile Val His Tyr Gly Asp Asp Gly Trp Ala Ser
                     600
                                                    605
Leu Asn Gly Leu Leu Lys Glu Ala His Thr Thr Ile Ser Ser Asn Asp 610 620
Arg Ala Ser Leu Ile Asn Asn Ala Phe Gln Leu Val Ser Ile Gly Lys
                    630
                                           635
Leu Ser Ile Glu Lys Ala Leu Asp Leu Ile Leu Tyr Leu Lys Asn Glu
645 650 655
Thr Glu Ile Met Pro Ile Phe Gln Gly Leu Asn Glu Leu Ile Pro Met 660 665 670
                                                      670
Tyr Lys Leu Met Glu Lys Arg Asp Met Val Glu Val Glu Thr Gln Phe 675 680 685
Lys Asp Phe Leu Leu Arg Leu Leu Lys Asp Leu Ile Asn Lys Gln Thr 690 695 700
Trp Thr Asp Glu Gly Ser Val Ser Glu Arg Met Leu Arg Ser Gln Leu 705 710 . 715 720
Leu Leu Leu Ala Cys Val His Arg Tyr Gln Leu Cys Val Gln Arg Ala
725 730 735
Glu Arg Tyr Phe Arg Glu Trp Lys Ala Ser Asn Gly Asn Met Ser Leu 740 745 750
Pro Ile Asp Val Thr Leu Ala Val Phe Ala Val Gly Ala Gln Asn Thr 755 760 765
Glu Gly Trp Asp Phe Leu Tyr Ser Lys Tyr Gln Ser Ser Leu Ser Ser 770 775 780
Thr Glu Lys Ser Gln Ile Glu Phe Ser Leu Cys Ile Ser Gln Asp Pro, 785 790 795 . . 800
Glu Lys Leu Gln Trp Leu Leu Asp Gln Ser Phe Lys Gly Glu Ile Ile
805 810 815
Lys Thr Gln Glu Phe Pro His Ile Leu Thr Leu Ile Gly Arg Asn Pro 820 825 830
Val Gly Tyr Pro Leu Ala Trp Lys Phe Leu Lys Glu Asn Trp Asn Lys
835 840 845
Ile Val Gln Lys Phe Glu Leu Gly Ser Ser Ser Ile Ala His Met Val
                         855
                                               860
Met Gly Thr Thr Asn Gln Phe Ser Thr Lys Ala Arg Leu Glu Lys Val
                      870
                                           875
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Val Gln Gln Thr Ile Glu Thr Ile Glu Lys Asn Ile Arg Trp Met Asp
            900
                              905
                                                  910
Lys Asn Phe Asp Lys Ile Arg Leu Trp Leu Gln Lys Lys Arg Gln Glu
       915
                          920
Leu Leu
  930
<210> 645
<211> 179
<212> PRT
<213> Rat
<400> 645
Met Leu His Asn Val Ser Lys Gly Val Val Tyr Ser Ala Thr Val Val
                                  10
Leu Gly Leu Leu Ala Tyr Val Ala Phe Lys Cys Trp Arg Ser Arg Lys
                               25
Gln Arg Gln Gln Leu Ala Lys Ala Arg Thr Val Glu Leu Gly Asp Pro
35 40 45
Asp Arg Asp Gln Arg His Gly Asp Ser Ser Ile Phe Val Asp Ser Pro 50 55 60
                                          60
His Gly Leu Glu Pro Cys Ile Pro Ser Gln Gly Pro His Ala Asp Leu
Gly Cys Arg Leu Tyr Leu His Ile Pro Gln Gln Gln Gln Glu Glu Val
              85
                                  90
Gln Arg Leu Leu Ile Leu Gly Glu Pro Ala Lys Gly Trp Gln Gly Leu
100 105 110
          100
                             105
Ala Gly Gln Leu Gly Tyr Gln Ala Glu Ala Val Glu Thr Met Ala Cys
       115
                         120
                                            125
Asp Gln Asp Pro Ala Tyr Ala Leu Leu Arg Asp Trp Ala Ala Gln Glu
130 135 140
Gly Ser Gly Ala Thr Leu Arg Val Leu Glu Asp Ala Leu Thr Ala Ile
145 150 155 160
                 150
                                     155
Gly Arg Glu Asp Val Val Gln Val Leu Ser Ser Pro Ala Glu Gly Cys
                                170
Ser Val Val
<210> 646
<211> 298
<212> PRT
<213> Rat
<400> 646
Met Lys Tyr Leu Leu Asp Leu Ile Leu Leu Pro Leu Leu Ile Val
1
                                  10
Phe Cys Ile Glu Ser Phe Ile Lys Arg Leu Ile Pro Lys Lys Lys Lys Lys 20 25 30
Ser Val Ala Gly Glu Ile Val Leu Ile Thr Gly Ala Gly His Gly Ile
35 40 45
Gly Arg Leu Thr Ala Tyr Glu Phe Ala Lys Leu Asn Thr Lys Leu Val
                      55
   50
                                          60
Leu Trp Asp Ile Asn Lys Asn Gly Ile Glu Glu Thr Ala Ala Lys Cys
                  70
                                     75
```

Arg Lys Leu Gly Ala Gln Val His Pro. Phe Val Val Asp Cys Ser Gln

```
85
Arg Glu Glu Ile Tyr Ser Ala Val Arg Lys Val Lys Glu Glu Val Gly
           100
                               105
                                                   110
Asp Val Ser Ile Leu Val Asn Asn Ala Gly Val Val Tyr Thr Ala Asp
115 120 125
Leu Phe Ala Thr Gln Asp Pro Gln Ile Glu Lys Thr Phe Glu Val Asn
                      135
   130
                                          140
Val Leu Ala His Phe Trp Thr Thr Lys Ala Phe Leu Pro Ala Met Met
145
          150
                                      155
                                                           160
Lys Asn Asn His Gly His Val Val Thr Val Ala Ser Ala Ala Gly His
Thr Val Val Pro Phe Leu Leu Ala Tyr Cys Ser Ser Lys Phe Ala Ala
180 185 190
Val Gly Phe His Arg Ala Leu Thr Asp Glu Leu Ala Ala Leu Gly Cys
195 200 205
Thr Gly Val Arg Thr Ser Cys Leu Cys Pro Asn Phe Ile Asn Thr Gly 210 215 220
                     215
                                        220
Phe Ile Lys Asn Pro Ser Thr Asn Leu Gly Pro Thr Leu Glu Pro Glu
225 230 235 240
                                      235
Glu Val Val Glu His Leu Met His Gly Ile Leu Thr Asn Gln Lys Met
              245
                         250 255
Ile Phe Val Pro Gly Ser Ile Ala Leu Leu Thr Val Leu Glu Arg Val
                         265
          260
                                                - 270
Phe Pro Glu Arg Phe Leu Asp Val Leu Lys His Arg Ile Asn Val Lys
                     280
     275
                                               285
Phe Asp Ala Val Val Gly Tyr Lys Asp Lys
   290
                       295
<210> 647
<211> 59
<212> PRT
<213> Rat
<400> 647
Met Asn Ser Val Pro Thr Gln Leu Ile Leu Val Leu Thr Ser Leu Leu
                                   10
Leu Ile Leu Pro Gly Val Glu Ala Val Glu Ala Gly Asp Ala Ile Ala
           20
                               25
                                                  30
Leu Leu Gly Val Val Leu Ser Val Thr Gly Ile Cys Ala Cys Leu
      35
                          40
Gly Ile Tyr Ala Arg Lys Arg Asn Gly Gln Ile
   50
                       55
<210> 648
<211> 281
<212> PRT
<213> Rat
<400> 648
Val Leu Ser Thr Ala Pro Pro Thr Met Arg Pro Ala Pro Gln Pro Gln
                5
                                   10
Asp Cys Pro Ala Ser Ile Cys Leu Asn Gly Gly Ser Cys Arg Val Gly 20 25 30
Ala Lys His His Leu Glu Cys Leu Cys Pro Glu Gly Phe Ile Gly Leu
                          40
                                              45
Typ Cys Glu Ser Pro Val Glu Gln Arg Thr Lys Pro Ser Ser Ile Pro 50 55 60
                       55
                                           60
```

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Asp Thr Pro Arg Pro Pro Arg Leu Leu Pro Leu Arg Ile Glu Pro Val
                    70
                                         75
Ser Pro Thr Ser Leu Arg Val Glu Leu Gln Arg Tyr Leu Gln Gly Asn
                85
                                     90
                                                          95
Thr Val Gln Leu Arg Ser Leu Arg Leu Thr Tyr Arg Asn Leu Ser Gly
100 105 110
           100 105
                                                110
Pro Asp Lys Arg Leu Val Thr Leu Arg Leu Pro Ala Ser Leu Ala Glu
115 120 125
Tyr Thr Val Thr Gln Leu Arg Pro Asn Ala Thr Tyr Ser Ile Cys Val
130 135 140
Thr Ala Leu Gly Ala Gly Arg Thr Pro Glu Gly Glu Glu Ala Cys Gly 145 150 155 160
Glu Ala Asn Thr Pro Gln Ala Val Arg Ser Asn His Ala Pro Val Thr 165 170 175
Gln Ala Arg Glu Gly Asn Leu Pro Leu Leu Ile Ala Pro Ala Leu Ala
           180
                         185
                                             190
Ala Val Leu Leu Ala Val Leu Ala Ala Ser Gly Ala Val Tyr Cys Val
       195
                   200
                                          205
Arg Arg Ala Arg Ala Ser Ser Thr Ala Gln Asp Lys Gly Gln Val Gly 210 215 220
Pro Gly Thr Gly Pro Leu Glu Leu Glu Gly Val Lys Val Pro Leu Glu 225 230 235 240
Pro Gly Ser Lys Ala Ser Glu Gly Gly Gly Glu Ala Leu Ser Gly Gly 245 250 255

Pro Glu Cys Glu Val Pro Leu Met Gly Tyr Pro Gly Pro Ser Leu Gln
                               265
           260
Gly Val Leu Pro Ala Gln Pro Tyr Ile
                             280
<210> 649
<211> 88
<212> PRT
<213> Rat
<400> 649
Leu Gly Ser Val Ser Val Thr Thr Ile Glu Pro Cys Val Gln Val Gly
            . 5
                                    10
Ser Pro Ala Arg His Ser Leu His Pro Pro Leu Cys Ile Ser Ile Gly
          20
                                25
                                                    30
Ala Thr Val Pro Tyr Phe Ala Glu Gly Ser Gly Gly Pro Val Pro Thr
       35
                           40
                                                 45
Thr Ser Ala Leu Ile Leu Pro Pro Glu Tyr Ser Ser Trp Gly Tyr Pro
    50
                       55
                                             60
Tyr Glu Ala Pro Pro Ser Tyr Glu Gln Ser Cys Gly Ala Gly Gly Thr
                    70
65
Asp Val Gly Leu Ile Pro Gly Ser
<210> 650
<211> 290
<212> PRT
<213> Rat
<400> 650
Glu Val Asp Pro Asp Leu Lys Cys Ala Leu Cys His Lys Val Leu Glu
1 , 5 10 15
Asp Pro Leu Thr Thr Pro Cys Gly His Val Phe Cys Ala Gly Cys Val
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Leu Pro Trp Val Val Gln Glu Gly Ser Cys Pro Ser Arg Cys Arg Gly 35 40 45
Arg Leu Ser Ala Lys Glu Leu Asn His Val Leu Pro Leu Lys Arg Leu 50 60
Ile Leu Lys Leu Asp Ile Lys Cys Ala His Ala Ala Arg Gly Cys Gly 65 70 75 80
Arg Val Val Lys Leu Gln Asp Leu Pro Glu His Leu Glu Arg Cys Asp
85 90 95
Phe Ala Pro Ala Arg Cys Arg His Ala Gly Cys Gly Gln Leu Leu Leu 100 105 110
Arg Arg Asp Val Glu Ala His Met Arg Asp Ala Cys Asp Ala Arg Pro
115 120 125
Val Gly Arg Cys Gln Glu Gly Cys Gly Leu Pro Leu Thr His Gly Glu
130 135 140
Gln Arg Ala Gly Gly His Cys Cys Ala Arg Ala Leu Arg Ala His Asn
145 150 155 160
Gly Ala Leu Gln Ala Arg Leu Gly Ala Leu His Lys Ala Leu Lys Lys
165 170 175
Glu Ala Leu Arg Ala Gly Lys Arg Glu Lys Ser Leu Val Ala Gln Leu
180 185 190
Ala Ala Gln Leu Glu Leu Gln Met Thr Ala Leu Arg Tyr Gln Lys
195 200 205
Lys Phe Thr Glu Tyr Ser Ala Arg Leu Asp Ser Leu Ser Arg Cys Val
210 215 220
Ala Ala Pro Pro Gly Gly Lys Gly Glu Glu Thr Lys Ser Val Thr Leu 225 230 235 240
Val Leu His Arg Asp Ser Gly Ser Leu Gly Phe Asn Ile Ile Gly Gly 245 250 255
Arg Pro Cys Val Asp Asn Gln Asp Gly Ser Ser Ser Glu Gly Ile Phe 260 265 270 .
Val Ser Lys Ile Val Asp Ser Gly Pro Ala Ala Lys Lys Arg Pro Ala
                               280
Asn Ser
    290
<210> 651
<211> 202
<212> PRT
<213> Rat
<400> 651
Met Ala Arg Pro Arg Pro Arg Glu Tyr Lys Ala Gly Asp Leu Val Phe 1 5 10 15
Ala Lys Met Lys Gly Tyr Pro His Trp Pro Ala Arg Ile Asp Glu Leu 20 25 30 .
Pro Glu Gly Ala Val Lys Pro Pro Ala Asn Lys Tyr Pro Ile Phe Phe 35 40 45
Phe Gly Thr His Glu Thr Ala Phe Leu Gly Pro Lys Asp Leu Phe Pro 50 55 60
Tyr Lys Glu Tyr Lys Asp Lys Phe Gly Lys Ser Asn Lys Arg Lys Gly 65 70 75 80
Phe Asn Glu Gly Leu Trp Glu Ile Glu Asn Asn Pro Gly Val Lys Phe 85 90 95
Thr Gly Tyr Gln Thr Ile Gln Gln Ser Ser Ser Glu Thr Glu Gly
            100
                                                          110
                                  105
```

Glu Gly Gly Asn Thr Ala Asp Ala Ser Ser Glu Glu Glu Gly Asp Arg

```
Val Glu Asp Gly Lys Gly Lys Arg Lys Asn Glu Lys Gly Gly Ser Lys
130 135 140
                                             140
   130
Arg Lys Lys Ser Tyr Thr Ser Lys Lys Ser Ser Lys Gln Ser Arg Lys 145 150 150 155 160
Ser Pro Gly Asp Glu Asp Asp Lys Asp Cys Lys Glu Glu Glu Asn Lys
165 170 175
Ser Ser Ser Glu Gly Gly Asp Ala Gly Asn Asp Thr Arg Asn Thr Thr
180 185 190
Ser Asp Leu Gln Lys Ala Gly Glu Gly Thr
                           200
<210> 652
<211> 79
<212> PRT '
<213> Rat
<400> 652
Met Pro Val Ala Val Gly Pro Tyr Gly Gln Ser Gln Pro Ser Cys Phe
1 5 10 15
Asp Arg Val Lys Met Gly Phe Val Met Gly Cys Ala Val Gly Met Ala 20 25 30
Ala Gly Ala Leu Phe Gly Thr Phe Ser Cys Leu Arg Ile Gly Met Arg 35 40 45
Gly Arg Glu Leu Met Gly Gly Ile Gly Lys Thr Met Met Gln Ser Gly 50 55 60
   50
                                             60
Gly Thr Phe Gly Thr Phe Met Ala Ile Gly Met Gly Ile Arg Cys
<210> 653
<211> 555
<212> PRT
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Met Pro Val Asn Leu Gly Gln Ala Leu Gly Leu Leu Pro Phe Leu Ala 1 5 10 15
Glu Leu Ala Asn Pro Glu Thr Alà Arg Gln Leu Phe Arg Gln Phe Arg 35 40 45
Tyr Gln Val Met Ser Gly Pro Gln Glu Thr Leu Arg Gln Leu Arg Lys 50 60
                       55
                                             60
Leu Cys Phe Gln Trp Leu Arg Pro Glu Val His Thr Lys Glu Gln Ile 65 70 75 80
Leu Glu Ile Leu Met Leu Glu Gln Phe Leu Thr Ile Leu Pro Gly Glu 85 90 95
Ile Gln Met Trp Val Arg Lys.Gln Cys Pro Gly Ser Gly Glu Glu Ala 100 105 110
Val Thr Leu Val Glu Ser Leu Lys Gly Asp Pro Gln Lys Leu Trp Gln 125 120 125
Trp Ile Ser Ile Gln Val Leu Gly Gln Glu Ile Pro Phe Glu Lys Glu 130 135 140
Asn Ser Ala Arg Cys Arg Gly Asp Lys Val Glu Pro Ala Leu Glu Ala
145 150 150 160
Glu Pro Thr Val Glu Val Val Pro Gln Asp Leu Pro Leu Gln Asn Thr
                165
                                     . 170
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Ser Ser Ala Pro Gly Glu Leu Leu Ser His Gly Val Lys Glu Glu Ser
             180
                                    185
Asp Met Glu Pro Glu Leu Ala Leu Ala Ala Ser Gln Leu Pro Ala Arg
                      200
                                                   205
Ser Glu Glu Arg Pro Thr Arg Asp Gln Glu Val Gly Thr Ala Leu Leu
210 215 220
Pro Ser Leu Gln Glu Glu Gln Trp Arg His Leu Asp Ser Thr Gln Lys
225 230 235 240
Glu Gln Tyr Trp Asp Leu Met Leu Glu Thr Tyr Gly Lys Met Val Ser
245 250 255
Gly Ala Gly Ile Ser Asn Ser Lys Pro Asp Leu Thr Asn Met Ala Glu 260 265 270
Tyr Gly Glu Glu Leu Val Gly Leu His Leu His Ser Ala Glu Lys Met 275 280 285
Ala Arg Ala Pro Cys Lys Glu Asp Arg Gln Glu Asn Asp Lys Glu Asn
290 295 300
Leu Asn Leu Glu Asn His Arg Asp Gln Gly Cys Leu Asp Val Phe Asp 305 310 315 320
Gln Ala Pro Gly Glu Ala Pro Pro Gln Thr Ala Leu Ser Asp Phe Phe 325 330 335
Gly Glu Ser Glu Pro His His Phe Gly Gly Glu Ser Val Pro Glu Ala
340 345 350
Leu Glu Asn Leu Gln Gly Glu Gly Thr Gly Ala His Leu Phe Pro His
355 360 365
                                                     365
Glu Arg Gly Ser Gly Lys Gln Leu Gly Gln His Ile Gln Ser Ser Ser 370 375 380
Ser Gly Glu Leu Ser Ala Leu Trp Leu Glu Glu Lys Arg Glu Ala Ser
385 390 395 400
Gln Lys Gly Gln Ala Arg Ala Pro Met Ala Gln Lys Leu Pro Thr Cys
405 410 415
Arg Glu Cys Gly Lys Thr Phe Tyr Arg Asn Ser Gln Leu Val Phe His
420 425 430
Gln Arg Thr His Thr Gly Glu Thr Tyr Fhe His Cys Arg Ile Cys Lys
435 440 445
Lys Ala Phe Leu Arg Ser Ser Asp Phe Val Lys His Gln Arg Thr His 450 460
Thr Gly Glu Lys Pro Cys Lys Cys Asp Tyr Cys Gly Lys Gly Phe Ser
465 470 475 480
                                                                   480
Asp Phe Ser Gly Leu Arg His His Glu Lys Ile His Thr Gly Glu Lys 485 490 495
Pro Tyr Lys Cys Pro Ile Cys Glu Lys Ser Phe Ile Gln Arg Ser Asn
500 505 510
Phe Asn Arg His Gln Arg Val His Thr Gly Glu Lys Pro Tyr Lys Cys
515 520 525
                                                    525
Thr His Cys Gly Lys Arg Phe Ser Trp Ser Ser Ser Leu Asp Lys His 530 535 540
Gln Arg Ser His Leu Gly Lys Lys Pro Cys Pro
545
                       550
                                             555
<210> 654
<211> 244
<212> PRT
<213> Rat
<400> 654
Leu Ala Tyr Tyr Asn Pro Phe Tyr Phe Leu Ser Ala Ala Ala Pro Gly
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Pro Gly Ala Ala Thr Ser Ala Gly Ala Thr Pro Thr Ala Val Ala Gly
                                  25
Leu Thr Ala Arg Ala Pro His Val Gln Ala Ser Ala Arg Ala Val Pro
                             40
Val Thr Arg Val Gly Ser Ala Ala Pro Ala Arg Thr Ala Ser Asp Thr
                      55
Gly Arg Gln Ala Gly Arg Glu Tyr Val Ile Pro Ser Leu Ala His Arg 65 70 75 80
                                       75
Phe Met Ala Glu Met Val Asp Phe Phe Ile Leu Phe Phe Ile Lys Ala
85 90 95
Thr Ile Val Leu Ser Ile Met His Leu Ser Gly Ile Lys Asp Ile Ser 100 105 110
Lys Phe Ala Met His Tyr Ile Ile Glu Glu Ile Asp Glu Asp Thr Ser
115 120 125
Met Glu Asp Leu Gln Lys Met Met Ile Val Ala Leu Ile Tyr Arg Leu
130 135 140
Leu Val Cys Phe Tyr Glu Ile Ile Cys Ile Trp Gly Ala Gly Gly Ala
           150
                                155
Thr Pro Gly Lys Phe Leu Leu Gly Leu Arg Val Val Thr Cys Asp Thr
165 170 175
Ser Val Leu Ile Ala Pro Ser Arg Val Leu Val Ile Pro Ser Ser Asn
180 185 190
Val Ser Ile Thr Thr Ser Thr Ile Arg Ala Leu Ile Lys Asn Phe Ser
195 200 205
Ile Ala Ser Phe Phe Pro Ala Phe Ile Thr Leu Leu Phe Phe Gln His 210 215 220
Asn Arg Thr Ala Tyr Asp Ile Val Ala Gly Thr Ile Val Val Lys Arg
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225
                                          235
Asn Gly Val Arg
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<210> 655
<211> 265
<212> PRT
<213> Rat

 400> 655
 Met Gly Leu Leu Leu Phe Leu Val Leu Leu Ser Pro Leu Ser Cys Val Leu 1
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Leu Glu Leu Arg Gly Val Val Phe Pro Tyr Gln Pro Arg Glu Gly Arg

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165
                             170
Tyr Gln Leu Asn Phe His Glu Ala Gln Gln Val Cys Gln Glu Gln Asp
             180
                         185
                                                190
Ala Val Val Ala Thr Phe Glu Gln Leu Phe Arg Ala Trp Glu Glu Gly 195 200 205
Leu Asp Trp Cys Asn Ala Gly Trp Leu Gln Asp Ala Ser Ser Cys Arg
210 215 220
Phe Gly Thr Ser Ser Cys Arg Ile Arg His Glu Ala Cys Arg Arg Pro 225 230 235 240
Leu Trp Cys Gly Asp Pro Arg Val Asn Pro Pro Thr Pro Cys Leu Thr 245 250 255
Arg Arg Gln Asn Leu Gln Leu Arg Thr
             260
<210> -656
<211> 343
<212> PRT
<213> Rat
<400> 656
Met Ala Val Cys Pro Tyr Gly Ala Ala Ala Val Val Met Ala Leu Leu 1 \hspace{1cm} 5 \hspace{1cm} 10 \hspace{1cm} 15
                 5
Ser Ala Ala Ile Ala Phe His Trp Ser Pro Leu Leu Ala Val Leu Gln 20 25 30
Arg Ala Leu Ser Leu His Thr Ala His Ala Thr Lys Asp Met Asp Asn 35 40 45
Leu Phe Gln Leu Val Arg Asn Ile Val Pro Ala Leu Thr Ser Lys Lys 50 55 60
                          55
His Lys Gly Gln Asp Gly Arg Ile Gly Ile Val Gly Gly Cys Gln Glu 65 70 75 80
Tyr Thr Gly Ala Pro Tyr Phe Ala Gly Ile Ser Ala Leu Lys Val Gly 85 90 95
Ala Asp Leu Thr His Val Phe Cys Ala Arg Glu Ala Ala Pro Val Ile
100 105 . 110
Lys Ser Tyr Ser Pro Glu Leu Ile Val His Pro Val Leu Asp Ser Ser 115 120 125
Asp Ala Val Glu Glu Val Lys Lys Trp Leu Pro Arg Leu His Ala Leu 130 135 140
Val Val Gly Pro Gly Leu Gly Arg Asp Asp Leu Leu Leu Asn Asn Val 145 150 155 160
Arg Gly Ile Leu Glu Ser Thr Lys Ala Arg Asp Ile Pro Val Val Ile
165 170 175
Asp Ala Asp Gly Leu Trp Leu Ile Ala Gln Arg Pro Ala Leu Val His
180 185 190
Gly Tyr Gln Lys Ala Val Leu Thr Pro Asn His Val Glu Phe Ser Arg
195 200 205.
Leu Trp Asp Ala Val Leu Ser Ser Pro Met Asp Thr Ser Asn His Ser 210 215 220
Gly Ser Val Leu Lys Leu Ser Gln Ala Leu Gly Asn Ile Thr Ile Val 225 230 235 240
Gln Lys Gly Glu Gln Asp Leu Ile Ser Asn Gly Gln Gln Val Leu Val
245 250 255
Cys Asn Gln Glu Gly Ser Ser Arg Arg Cys Gly Gly Gln Gly Asp Leu
260 265 270
Leu Ser Gly Ser Leu Gly Val Met Ala His Trp Ala Leu Arg Ala Gly
```

280

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Pro Glu Lys Thr Asn Gly Ser Ser Pro Leu Leu Val Ala Ala Trp Gly
    290
                        295
                                            300
Ala Cys Thr Leu Thr Arg Glu Cys Asn His Leu Ala Phe Gln Lys Tyr
305
           310
                                      315
Gly Arg Ser Thr Thr Thr Thr Asp Met Ile Ala Glu Val Gly Ala Ala
             325
                                     330
Phe Ser Lys Leu Phe Thr Thr
            340
<210> 657
<211> 61
<212> PRT
<213> Rat
<400> 657
Met Pro Cys Trp Ser Leu Tyr Gln Leu Met Val Leu Tyr Gln Ile Ile
                                    10
Ile Leu Phe Phe Leu Phe Lys Gln Val Ser Val Arg Thr Cys Tyr Leu
20 25 30
Ser Thr Glu Gly Lys Pro Cys Gly Ser Val Leu Phe Ala Cys Lys Ser
  35
                           40 45
Leu Gln Gln Cys Leu Leu Thr Val Leu Val Thr Pro Val
                       55
<210> 658
<211> 1172
<212> PRT
<213> Rat
Met Leu Trp Ala Leu Ala Leu Leu Ala Leu Gly Ile Gly Pro Arg Ala
Tyr Ala Gly Asp His Gly Glu Asp Thr Ala Phe Asp Leu Phe Ser Ile
20 25 30
Ser Asn Ile Asn Arg Lys Thr Ile Gly Ala Lys Gln Phe Arg Gly Pro
      35
                            40
                                                45
Asp Pro Gly Val Pro Ala Tyr Arg Phe Val Arg Phe Asp Tyr Val Pro
 . 50
                       55
                                            60
Pro Val Asn Thr Asp Asp Leu Asn Arg Ile Val Lys Leu Ala Arg Arg 65 70 75 80
Lys Glu Gly Phe Phe Leu Thr Ala Gln Leu Lys Gln Asp Arg Lys Ser
Arg Gly Thr Leu Leu Val Leu Glu Gly Pro Gly Thr Ser Gln Arg Gln 100 105 110
Phe Glu Ile Val Ser Asn Gly Pro Gly Asp Thr Leu Asp Leu Asn Tyr 115 120 125
Trp Val Glu Gly His Gln His Thr Asn Phe Leu Glu Asp. Val Gly Leu
130 135 140
Ala Asp Ser Gln Trp Lys Asn Val Thr Val Gln Val Ala Ser Asp Thr
145 150 155 160
                                       155
Tyr Ser Leu Tyr Val Gly Cys Asp Leu Ile Asp Ser Val Thr Leu Glu
165 170 175
Glu Pro Phe Tyr Glu Gln Leu Glu Ala Asp Lys Ser Arg Met Tyr Val
180 185 190
Ala Lys Gly Ala Ser Arg Glu Ser His Phe Arg Gly Leu Leu Gln Asn 195 200 205
Val His Leu Val Phe Ala Asp Ser Val Glu Asp Ile Leu Ser Lys Lys
```

```
215
                                                       220
Gly Cys Gln His Ser Gln Gly Ala Glu Val Asn Thr Ile Ser Glu His
                        230
                                                 235
Thr Glu Thr Leu His Leu Ser Pro His Ile Thr Thr Asp Leu Val Val 245 250 255
Gln Gly Val Glu Lys Ala Gln Glu Val Cys Thr His Ser Cys Glu Glu 260 265 270

Leu Ser Asn Met Met Asn Glu Leu Ser Gly Leu His Val Met Val Asn 275 280 285
Gln Leu Ser Lys Asn Leu Glu Arg Val Ser Ser Asp Asn Gln Phe Leu
290 295 300
Leu Glu Leu Ile Gly Gly Pro Leu Lys Thr Arg Asn Met Ser Ala Cys 305 310 315 320
Val Gln Glu Gly Arg Ile Phe Ala Glu Asn Glu Thr Trp Val Val Asp 325 330 335
Ser Cys Thr Thr Cys Thr Cys Lys Lys Phe Lys Thr Val Cys Asn Gln 340, 345 350
        340,
Ile Thr Cys Ser Pro Ala Thr Cys Ala Asn Pro Ser Leu Val Glu Gly 355 . 360 365
Glu Cys Cys Pro Ser Cys Ser His Ser Ala Asp Asn Asp Glu Gly Trp 370 380
Ser Pro Trp Ala Glu Trp Thr Glu Cys Ser Val Thr Cys Gly Ser Gly 385 390 395 ... 400
Thr Gln Gln Arg Gly Arg Ser Cys Asp Val Thr Ser Asn Thr Cys Leu
405 410 415
Gly Pro Ser Ile Gln Thr Arg Thr Cys Ser Leu Gly Lys Cys Asp Thr 420 425 430
Arg Ile Arg Gln Asn Gly Gly Trp Ser His Trp Ser Pro Trp Ser Ser
435 440 445
Cys Ser Val Thr Cys Gly Val Gly Asn Val Thr Arg Ile Arg Leu Cys
450 455 460
Asn Ser Pro Val Pro Gln Met Gly Gly Lys Asn Cys Lys Gly Ser Gly 465 470 475 480
Arg Glu Thr Lys Ala Cys Gln Arg Ala Pro Cys Pro Ile Asp Gly Arg
485 490 495
Trp Ser Pro Trp Ser Pro Trp Ser Ala Cys Thr Val Thr Cys Ala Gly 500 505 510
Gly Ile Arg Glu Arg Thr Arg Val Cys Asn Ser Pro Glu Pro Gln Tyr
515 520 525
Gly Cly Lys Asp Cys Val Gly Asp Val Thr Glu His Gln Met Cys Asn
530 535 540
Lys Arg Ser Cys Pro Ile Asp Gly Cys Leu Ser Asn Pro Cys Phe Pro 545 550 555 560
Gly Ala Lys Cys Asn Ser Phe Pro Asp Gly Ser Trp Ser Cys Gly Ser
565 570 575
Cys Pro Val Gly Phe Leu Gly Asn Gly Thr His Cys Glu Asp Leu Asp. 580 585 -590
Glu Cys Ala Val Val Ala Asp Ile Cys Phe Ser Ile Asn Lys Ala Ser 595 600 605
Arg Cys Val Asn Thr Asn Pro Gly Phe His Cys Leu Pro Cys Pro Pro 610 \phantom{\bigg|} 615 \phantom{\bigg|} 620 \phantom{\bigg|} .
Arg Tyr Lys Gly Thr Gln Pro Phe Gly Ile Gly Leu Glu Asp Ala Lys 625 630 635 640
Thr Glu Lys Gln Val Cys Glu Pro Glu Asn Pro Cys Lys Asp Lys Thr
645 650 655
His Asn Cys His Lys His Ala Glu Cys Ile Tyr Leu Gly His Phe Ser
                                        665.
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```
Asp Pro Met Tyr Lys Cys Glu Cys Gln Thr Gly Tyr Ala Gly Asp Gly
         675
                                 680
                                                         685
Leu Ile Cys Gly Glu Asp Ser Asp Leu Asp Gly Trp Pro Asn Ser Asn 690 695 700
Leu Val Cys Ala Thr Asn Ala Thr Tyr His Cys Val Lys Asp Asn Cys 705 710 715 720
Pro Lys Leu Pro Asn Ser Gly Gln Glu Asp Phe Asp Lys Asp Gly Ile
725 730 735
Gly Asp Ala Cys Asp Glu Asp Asp Asp Asp Asp Cly Val Ser Asp Glu 740 745 750
Lys Asp Asn Cys Pro Leu Leu Phe Asn Pro Arg Gln Leu Asp Tyr Asp 755 760 ,765
Lys Asp Glu Val Gly Asp Asp Cys Asp Asn Cys Pro Tyr Val His Asn 770 775 780
Gln Ala Gln Ile Asp Thr Asp Asn Asn Gly Glu Gly Asp Ala Cys Ser
785 790 795 800
Val Asp Ile Asp Gly Asp Asp Val Phe Asn Glu Arg Asp Asn Cys Pro
805 810 815
Tyr Val Tyr Asn Thr Asp Gln Arg Asp Thr Asp Gly Asp Gly Val Gly 820 825 830
Asp His Cys Asp Asn Cys Pro Leu Met His Asn Pro Asp Gln Met Asp 835 840 845
Gln Asp Asn Asp Leu Val Gly Asp Gln Cys Asp Asn Asn Glu Asp Ile
850 855 860
Asp Asp Asp Gly His Gln Asn Asn Gln Asp Asn Cys Pro Tyr Ile Ser
865 870 875 880
Asn Ser Asn Gln Ala Asp His Asp Asn Asp Gly Lys Gly Asp Ala Cys
885 890 895
Asp Ser Asp Asp Asp Asp Asp Gly Val Pro Asp Asp Asp Asp Asn Cys 900 905 910
Arg Leu Val Phe Asn Pro Asp Gln Lys Asp Ser Asp Gly Asp Gly Arg 915 920 925
Gly Asp Ile Cys Lys Asp Asp Phe Asp Asn Asp Asn Val Pro Asp Ile
930 935 940
Asp Asp Val Cys Pro Glu Asn Asn Ala Ile Thr Glu Thr Asp Phe Arg 945 950 955 960
Asn Phe Gln Met Val Pro Leu Asp Pro Lys Gly Thr Thr Gln Ile Asp
965 970 975
Pro Asn Trp Val Ile Arg His Gln Gly Lys Glu Leu Val Gln Thr Ala 980 985 990
Asn Ser Asp Pro Gly Ile Ala Val Gly Phe Asp Glu Phe Gly Ser Val 995 1000 1005
Asp Phe Ser Gly Thr Phe Tyr Val Asn Thr Asp Arg Asp Asp Asp Tyr 1010 1015 1020
Ala Gly Phe Val Phe Gly Tyr Gln Ser Ser Ser Arg Phe Tyr Val Val 1025 1030 1035 1040
Met Trp Lys Gln Val Thr Gln Thr Tyr Trp Glu Asp Lys Pro Ser Arg
1045 1050 1055
Ala Tyr Gly Tyr Ser Gly Val Ser Leu Lys Val Val Asn Ser Thr Thr
1060 1065 1070
Gly Thr Gly Glu His Leu Arg Asn Ala Leu Trp His Thr Gly Asn Thr
1075 1080 1085
Glu Gly Gln Val Arg Thr Leu Trp His Asp Pro Lys Asn Ile Gly Trp
1090 1095 1100
Lys Asp Tyr Thr Ala Tyr Arg Trp His Leu Ile His Arg Pro Lys Thr
                     1110
                                             1115
Gly Tyr Met Arg Val Leu Val His Glu Gly Lys Gln Val Met Ala Asp
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1125
                                     1130
Ser Gly Pro Ile Tyr Asp Gln Thr Tyr Ala Gly Gly Arg Leu Gly Leu
                       1145 1150
           1140
Phe Val Phe Ser Gln Glu Met Val Tyr Phe Ser Asp Leu Lys Tyr Glu
      1155
                              1160
Cys Arg Asp Ala
  · 1170
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                      25
Ser Ser Val Val Ser Glu Ser Ala Val Ser Trp Ala Ala Gly Thr Glu 35 40 45
Ala Val Leu Arg Cys Gln Ser Pro Arg Met Val Trp Thr Gln Asp Arg 50 55 60
Leu His Asp Arg Gln Arg Val Val His Trp Asp Leu Ser Gly Gly Pro 65 70 75 80
Gly Ser Gln Gly Arg Arg Leu Val Asp Met Tyr Ser Ala Gly Glu Gln
85 90 95
Arg Val Tyr Gln Pro Arg Asp Arg Asp Arg Leu Leu Leu Ser Pro Ser
100 105 110
Ala Phe His Asp Gly Asn Phe Ser Leu Leu Ile Arg Ala Val Glu Arg
115 120 125
Gly Asp Glu Gly Val Tyr Thr Cys Asn Leu His His His Tyr Cys His
130 135 140
Leu Tyr Glu Ser Leu Ala Val Arg Leu Glu Val Thr Asp Asp Pro Leu 145 150 150 160
Leu Ser Arg Ala Tyr Trp Asp Gly Glu Lys Glu Val Leu Val Val Ala
165 170 175
Leu Gly Ala Pro Ala Leu Met Thr Cys Val Asn Arg Glu His Leu Trp
. 180 185 190
Thr Asp Arg His Leu Glu Glu Ala Gln Gln Val Val His Trp Asp Arg
195 200 205
Gln Leu Pro Gly Val Pro His Asp Arg Ala Asp Arg Leu Leu Asp Leu
210 215 220
Tyr Ala Ser Gly Glu Arg Arg Ala Tyr Gly Pro Pro Phe Leu Arg Asp 225 230 235 240
Arg Val Ser Val Asn Thr Asn Ala Phe Ala Arg Gly Asp Phe Ser Leu 245 250 255 ,
Arg Ile Asp Asp Leu Glu Pro Ala Asp Glu Gly Ile Tyr Ser Cys His
260 265 270
Leu His His His Tyr Cys Gly Leu His Glu Arg Arg Val Phe His Leu 275 280 285
Arg Val Thr Glu Pro Val Phe Glu Pro Pro Ala Arg Ala Ser Pro Gly 290 295 300
Asn Gly Ser Gly His Asn Ser Val Pro Ser Pro Asp Pro Thr Met Ala 305 310 315 320
Arg Gly His Ser Ile Ile Asn Val Ile Val Pro Glu Asp His Thr His
                325
                          330
Phe Phe Gln Gln Leu Gly Tyr Val Leu Ala Thr Leu Leu Leu Phe Ile
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Leu Leu Leu Ile Thr Val Val Leu Ala Thr Arg His Arg His Ser Gly
                             360
       355
Gly Cys Lys Thr Ser Asp Arg Lys Ala Gly Lys Ser Lys Gly Lys Asp 370 380
                                                380
Val Asn Met Met Glu Phe Ala Ile Ala Thr Arg Asp Gln Ala Pro Tyr
385 390 395 400
Arg Thr Glu Asp Ile Gln Leu Asp Tyr Lys Asn Asn Ile Leu Lys Glu
405 410 415
                                     410
Arg Ala Gly Leu Ala His Ser Pro Leu Pro Ala Lys Asp Val Asp Leu
            420
                               425
Asp Lys Glu Phe Arg Lys Glu Tyr Cys Lys
        435
                               440
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<213> Rat
<400> 660
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Gln Gly Gln Leu Leu Phe Ser Cys Pro Trp Ser Cys Ile Thr Ser Thr 35 40 45
His Thr Phe Ile Ala Ser Ser Thr Val Leu Pro Gly Lys Val Gln Ala
   50
                      55
Pro Phe Ser Arg Val Leu Gln Leu Val Arg Gly Arg Ala Ser Ser Pro 65 70 75 80
Lys Leu Met Thr Leu Trp Gly Ala Phe Pro Pro Ala Arg Gly Asp Glu
85 90 95
               85
Val Leu Gly Arg Gly Trp Asn Ile Thr Ser Val Pro Leu Pro Ser His
100 105 110
Ser Arg Gln Val Ala Gly Ser Ala Ser His Thr His Thr Leu Gly Ala
        115
                            120
                                                  125
Ala Ser Pro Thr Pro Leu Ser Pro Gly Pro Ala Pro Leu Cys Ser Thr . 130 135 140
Met Leu Pro Gly Gln Gly Thr Gly Pro Thr Leu Pro Ser Ala Gly Thr 145 150 155 160
                                         155 .
                    150
Val Pro Ala Leu Pro Ser Ala Ala Thr Gly Glu Gly Trp Gly Gln Val
165 170 175

Ser Arg Gly Pro His Pro Val Arg Asp Gly Val Val His Ile Pro Trp
180 185 190
Thr Cys Thr Trp Cys Leu Met Ala Ala Pro Thr Arg Asn Thr Pro Met
      195
                             200
                                                    205
Ser Ser Ile Gly Asn Met Ser His Gly His
   210
                          215
<210> 661
<211> 108
<212> PRT
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Met Ser Leu Ile Gln Ala Ile Val Tyr Lys Val His Ser Phe Ser Cys
                                      , 10
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<210> 662 <211> 516 <212> PRT <213> Rat

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295

300

Arg Thr Lys Pro Asn Gln Glu Ala Ala Ala Pro Lys Val Leu Phe Thr

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310
                                           315
Gly Val Val Asp Ser Arg Gly Glu Arg Ala Val Leu Ala Leu Gly Gly
                325
                                      330
Ser Leu Ala Ser Ser Val Asn Glu Ala Ser His Leu Val Thr Asp Arg 340 345 350
Leu Pro Pro Asp Asp Tyr Leu Val Thr Asp Pro Glu Gln Glu Lys Asn 385 390 395 400
Phe Ser Phe Ser Leu Arg Asp Ser Leu Ser Arg Ala Arg Glu Arg Arg 405 410 415
                                                         415
Leu Leu Glu Asp Tyr Glu Ile His Val Thr Pro Gly Val Gln Pro Pro 420 425 430
Pro Pro Gln Met Gly Glu Ile Ile Ser Cys Cys Gly Gly Thr Val Leu
       435
                    440
Pro Ser Met Pro His Ser Tyr Lys Leu His Arg Val Val Ile Thr Cys 450 455 460
Thr Glu Asp Leu Pro Arg Cys Ala Ile Ala Ser Arg Leu Gly Leu Pro 465 470 480
Leu Leu Ser Pro Glu Phe Leu Leu Thr Gly Val Leu Lys Gln Glu Ala 485 490 495
Thr Pro Glu Ala Trp Ser Ser Pro Ile Trp Lys Cys Ser Leu Pro Lys
          500
                                  505
Lys Lys Lys Lys
        515
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<213> Rat
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Arg Glu Leu Leu Val Pro Gln Ala Glu Val Thr Ala Arg Ser Leu Arg
20 25 30
Leu Gln Trp Val Pro Gly Ser Asp Gly Ala Ser Pro Ile Arg Tyr Phe 35 \hspace{1cm} 40 \hspace{1cm} 45
Thr Val Gln Val Arg Glu Leu Pro Gly Gly Glu Trp Gln Thr Tyr Ser 50 55 60
Ser Ser Ile Ser His Glu Ala Thr Leu Cys Ala Val Glu Arg Leu Arg
65 70 75 80
Pro Phe Thr Ser Tyr Lys Leu Arg Leu Lys Ala Thr Asn Asp Ile Gly. 85 90 - 95
Asp Ser Asp Phe Ser Ala Glu Thr Glu Ala Val Thr Thr Leu Gln Asp 100 105 110
Val Pro Gly Glu Pro Pro Gly Ser Val Ser Ala Thr Pro His Thr Thr
115 120 125
Ser Ser Val Leu Ile Gln Trp Gln Pro Pro Arg Asp Glu Ser Leu Asn
130 135 140
Gly Leu Leu Gln Gly Tyr Arg Ile Tyr Tyr Arg Glu Leu Glu Ser Glu
145 150 155 160
Thr Gly Leu Ser Pro Glu Pro Lys Thr Leu Lys Ser Pro Ser Ala Leu
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.170

165

```
Arg Ala Glu Leu Thr Ala Gln Ser Ser Phe Lys Thr Val Asn Ser Ser
             180
                                    185
                                                            190
Ser Thr Leu Thr Thr Tyr Glu Leu Thr His Leu Lys Lys Tyr Arg Arg
        195 .
                               200
Tyr Glu Val Ile Met Thr Ala Tyr Asn Ile Ile Gly Glu Ser Pro Ala 210 215 220
Ser Val Pro Val Glu Val Phe Val Gly Glu Ala Ala Pro Ala Met Ala
225 230 235 240
Pro Gln Asn Ile Gln Val Thr Pro Leu Thr Ala Ser Gln Leu Glu Val
245 250 255
Thr Trp Asp Pro Pro Pro Pro Glu Ser Gln Asn Gly Asn Ile Gln Gly 260 265 270
Tyr Lys Val Tyr Tyr Trp Glu Ala Asp Ser Arg Asn Glu Thr Glu Lys
275 280 285
Met Lys Val Leu Phe Leu Pro Glu Pro Val Val Lys Ile Lys Asp Leu
290 295 300
Thr Ser His Thr Lys Tyr Leu Val Ser Ile Ser Ala Phe Asn Ala Ala 305 310 315 320
Gly Asp Gly Pro Arg Ser Asp Pro Cys Gln Gly Arg Thr His Gln Ala
325 330 335
Ala Pro Gly Pro Pro Ser Phe Leu Glu Phe Ser Glu Ile Thr Ser Thr 340 345 350
Thr Leu Asn Val Ser Trp Gly Glu Pro Ser Ala Ala Asn Gly Ile Leu
355 360 365
Gln Gly Tyr Arg Val Val Tyr Glu Pro Leu Ala Pro Val Gln Gly Val
370 375 380
Ser Lys Val Val Thr Val Asp Val Lys Gly Asn Trp Gln Arg Trp Leu
385 390 395 400
Lys Val Arg Asp Leu Thr Lys Gly Val Thr Tyr Phe Phe Arg Val Gln 405 . 410 415
Ala Arg Thr Ile Ala Tyr Gly Pro Glu Leu Gln Ala Asn Val Thr Ala 420 425 430
Gly Pro Ala Glu Gly Ser Pro Gly Ser Pro Arg Asn Val Leu Val Thr
435 440 445
Lys Ser Ala Ser Glu Leu Thr Leu Gln Trp Thr Glu Gly Asn Thr Gly 450 455 460
Asn Thr Pro Thr Thr Gly Tyr Val Ile Glu Ala Arg Pro Ser Asp Glu
465 470 475 480
Gly Leu Trp Asp Met Phe Ala Lys Asp Ile Pro Arg Ser Ala Thr Ser
485 490 495
Tyr Thr Val Gly Leu Asp Lys Leu Arg Gln Gly Val Thr Tyr Glu Phe 500 505 510
Arg Val Val Ala Val Asn Lys Ala Gly Phe Gly Glu Pro Ser Arg Pro 515 520 525
Ser Ile Ala Val Ser Ala Gln Ala Glu Ala Pro Phe Tyr Glu Glu Trp 530 540
Trp Phe Leu Leu Val Ile Ala Leu Ser Ser Leu Leu Leu Val Leu 545 550 555 560
Val Val Phe Val Leu Val Leu His Gly Gln Ser Lys Lys Tyr Lys Asn
565 570 575
Cys Gly Ser Gly Lys Gly Ile Ser Asn Met Glu Glu Thr Val Thr Leu
580 585 590
Asp Asn Gly Gly Phe Ala Ala Leu Glu Leu Asn Ser Arg His Leu Asn
      595
                 600 605
Val Lys Ser Thr Phe Ser Lys Lys Asn Gly Thr Arg Ser Pro Pro Arg
610 615 620
Pro Ser Pro Gly Gly Leu His Tyr Ser Asp Glu Asp Ile Cys Asn Lys
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630

```
Tyr Asn Gly Ala Val Leu Thr Glu Ser Val Asn Leu Lys Glu Lys Ser
                645
                                  650
                                                              655
Val Asp Gly Ser Glu Ser Glu Ala Ser Asp Ser Asp Tyr Glu Glu Ala
660 665 670
Leu Pro Lys His Ser Phe Val Asn His Tyr Met Ser Asp Pro Thr Tyr 675 680 685
Tyr Asn Phe Trp Lys Arg Arg Pro Pro Ala Ala Ala Pro His Arg Tyr 690 695 700
Glu Ala Val Ala Gly Ala Glu Ala Gly Pro His Leu His Thr Val Ile
705 710 715 720
Thr Thr Gln Ser Ala Gly Gly Val Tyr Thr Pro Ala Gly Pro Gly Ala 725 730 735
Arg Ala Pro Leu Thr Gly Phe Ser Ser Phe Val
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<212> PRT
<213> Rat
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Phe Cys Ser Leu Cys Val Glu Ala Glu Val Lys Glu Val Asn Ala Met 20 25 30
Val Gly Ser Asp Val Glu Leu Arg Cys Val Tyr Pro Arg Arg Ser His
Phe Ser Leu Asp Asp Leu Tyr Val Tyr Trp Gln Ile Val Asp Glu Ala 50 55 60
Lys Thr Val Val Thr Tyr Tyr Leu Pro Ser Ala Asn Glu Ser Ser Thr 65 70 75 80
The His Val Ser Asn Ser Tyr Lys Asn Arg Ala His Leu Ser Pro Asp
85 90 95
Leu Met Lys Glu Gly Asp Phe Ser Leu His Leu Gln Asn Val Thr Pro
100 105 110
Gln Asp Thr Gln Glu Phe Lys Cys Leu Val Phe Arg Met Ser Thr Val
115 120 125
Leu Gly Lys Ala Leu Glu Glu Val Val Arg Leu Arg Val Ala Ala Asn
130
135
140
Phe Ser Thr Pro Val Ile Ser Thr Ser Gly Ser Ser Asp Pro Gly Gln 145 150 150 160
Glu Arg Thr Phe Thr Cys Met Ser Lys Asn Gly Tyr Pro Glu Pro Asn
165 170 175
Leu Tyr Trp Ile Asn Arg Thr Asp Asn Thr Leu Ile Asp Glu Thr Leu 180 185 190
Gln Asn Asn Thr Val Tyr Leu Asn Glu Leu Gly Leu Tyr Asp Val Val 195 200 205
Ser Thr Leu Arg Ile Pro Trp Thr Pro His Val Asp Val Ile Cys Cys 210 215 220
Val Glu Asn Val Ala Leu His Gln Asn Ile Thr Ser Ile Ser Arg Ala
225 230 235 240
Asp Ser Phe Thr Gly Ser Met Asn Thr Glu Arg Pro Glu Glu Ile His 245 250 255.
Arg Glu Ala Thr Lys Val Leu Phe Tyr Ala Leu Ala Ala Leu Leu Ala 260 265 270
Val Val Val Ile Phe Ile Ile Val Leu Tyr Arg Cys Arg Arg Arg
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280

285

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Pro Cys Gln Ser Tyr Thr Gly Pro Arg Ala Val Gln Leu Glu Leu Thr
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                           295
                                                 300
Asp His Ser
305
<210> 665
<211> 143
<212> PRT
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Val Leu Phe Thr Lys Glu Leu Ser Arg Arg Leu Gln Gly Thr Gly Val 20 25 30
Thr Val Asn Ala Leu His Pro Gly Val Ala Arg Thr Glu Leu Gly Arg
     35
                            40
                                                   45
His Thr Gly Met His Asn Ser Ala Phe Ser Gly Phe Met Leu Gly Pro 50 55 60
Phe Phe Trp Leu Leu Phe Lys Ser Pro Gln Leu Ala Ala Gln Pro Ser 65 70 75 80
Thr Tyr Leu Ala Val Ala Glu Glu Leu Glu Ser Val Ser Gly Lys Tyr
85 90 95
Phe Asp Gly Leu Arg Glu Lys Ala Pro Ser Pro Glu Ala Glu Asp Glu
100 105 110
Glu Val Ala Arg Arg Leu Trp Thr Glu Ser Ala His Leu Val Gly Leu
    115
                             120
                                                  125
Asp Met Ala His Gly Ser Ser Gly Arg Gly His Ser Ile Ser Arg
   130
                          135
                                                 140
<210> 666
<211> 298
<212> PRT
<213> Mouse
<400> 666
Met Glu Ser Ala Asn Thr Leu Cys Pro Gly Arg Lys Cys Lys Gly Gly 1 5 10 15
Val Leu Ala His Leu Glu Arg Leu Glu Ala Gln Thr Asn Ile Ser Asn
20 25 30
Arg Lys Ser Glu Glu Pro Ala Val Arg Lys Lys Glu Ser Ser Leu Arg 35 40 45
Thr Lys Ile Arg Glu Leu Arg Gln Gln Arg Asp Lys Leu Arg Ala Glu
                         55
   50
Val Lys Gln Trp Gly Ala Arg Val Lys Glu Pro Pro Ala Lys Glu Asp
65 70 75 . 80
Pro Ser Arg Thr Val Ile Ser Glu Gln Glu Val Leu Glu Arg Glu Trp
85 90 95
Arg Asn Val Asp Ala Ile Leu Glu Ala Tyr Arg Phe Thr Gly Leu Ser
100 105 110
Gly Lys Leu Thr Ser Arg Gly Val Cys Met Cys Ile Ser Thr Ala Phe
115 120 125
Glu Gly Asn Leu Leu Asp Ser Tyr Phe Val Asp Leu Val Ile Glu Lys
130 135 140
                                                140
Pro Leu Arg Ile His His Ser Val Pro Val Phe Ile Pro Leu Glu
                      150
                                            155
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Lys Ile Ala Ala Ala His Leu Gln Thr Asp Val Gln Arg Phe Leu Phe
                  165
                                       170
Arg Leu Trp Glu Tyr Leu Asn Ala Tyr Ala Gly Arg Lys Tyr Gln Ala
180 185 190
Asp Gln Leu Glu Ser Asp Phe Cys Asp Val Leu Thr Gly Pro Leu Gln 195 200 205
Arg Asn Ala Leu Cys Asn Leu Leu Ser Phe Thr Tyr Lys Val Glu Gln 210 215 220
Arg Cys Gln Thr Phe Ser Phe Ser Ala Arg Leu Leu Tyr Glu Asp Pro 225 230 235 240

Thr Ala Ala Leu Pro Thr Asn Val Thr Val Thr Arg Pro Gly Val Glu 245 250 255
Ala Ser Ser Pro Pro Trp Glu Glu His Arg Ala Ser His Gln Met Leu
260 265 270
Phe Arg Thr Lys Pro Leu His Lys Val Phe Ala Ser Phe Ser Lys Glu
275 280 285
Thr Glu Lys Leu His Leu Asn Leu Val Ser
    290
                          295
<210> 667
<211> 226
<212> PRT.
<213> Mouse
<400> 667
Met Glu Ala Glu Leu Gly Gly Ser Phe Ile Lys Leu Arg Gln Ala Leu
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                                                               15
Phe Gln Leu Asn Ser Val Asp Ser Ser Leu Leu Phe Thr Ala Gln Ala
             20
                                   25
Leu Leu Arg Trp His Asp Gly His Gln Phe Cys Ser Lys Ser Gly Gln 35 40 45
Lys Ile Ile Tyr Tyr Pro Gln Met Ala Pro Val Val Ile Thr Leu Val 65 70 75 80
Ser Asp Gly Ala Arg Cys Leu Leu Ala Arg Gln Ser Ser Phe Pro Lys
85 90 95
Gly Leu Tyr Ser Ala Leu Ala Gly Phe Cys Asp Ile Gly Glu Ser Val
Glu Glu Thr Val His Arg Glu Val Ala Glu Glu Val Gly Leu Glu Val
115 120 125
Glu Asn Ile Gln Tyr Ser Ala Ser Gln His Trp Pro Phe Pro Asn Ser
130 135 140
Ser Leu Met Ile Ala Cys His Ala Thr Val Lys Pro Gly His Thr Glu
145 150 155 160
Ile Gln Val Asn Leu Lys Glu Leu Glu Ala Ala Ala Tro Phe Ser Leu
165 170 175
Asp Glu Val Thr Thr Ala Leu Arg Arg Lys Gly Ser Leu Ala Leu Gln
180 185 190
Pro Ser Glu Ala Ser Pro Leu Leu Leu Pro Pro Lys Leu Ala Ile Ala
195 200 205
His His Leu Ile Lys Lys Trp Val Glu Thr Arg Ser Cys Ser Ser Leu
    210
                          215
                                                 220
Ala Ala
225
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<210> 668

<211> 781 <212> PRT <213> Mouse <400> 668 Met Glu Met Met Lys Lys Leu Ile Ala Gly Gln Gly Pro Glu Pro Gln 1 10 15 Pro Ser Asn Arg Pro Thr Ser Arg Leu Gly Gly Ser Leu Leu Phe Gly 25 Asn Leu Val Pro Ala Asn Lys Asp Ala Pro Ala Leu Glu Pro Leu Gly 35 40 Thr Lys Leu Ser Ala Leu Pro Pro His Gly Ala Pro Gly Val Arg Lys 50 55 60 Val Pro Gly Gln Leu Pro Leu Leu Cys Ser Gly Arg Pro Pro Pro Glu 65 70 . 75 80 Lys Pro Ala Pro Ile Glu Pro Pro Glu Gly Trp Ser Pro Ala Pro Lys 85 90 95 Thr Gln Gly Lys Leu Asn Thr Arg Pro Gly Lys Val Ile Leu Fhe Ser 100 105 110 Glu Pro Gly Cys Arg Gly Arg Gly Arg Glu Val Trp Gly Asp Ile Ala 115 120 125 Asp Ala Ser Ala Trp Asp Pro Val Ala Ser Ile Arg Val Ile Arg Gly 130 135 140 Cys Trp Ile Leu Tyr Glu Gln Pro Glu Phe Arg Gly Gln Lys Leu Ser 145 150 155 160 Leu Pro Glu Gly Asp Val Glu Leu Arg Ala Leu Ala Cys Ala Trp Ser 165 170 175 Leu Gln Gly Phe Gly Ser Leu Arg Arg Ala Val Gln Asp Tyr Cys Thr 180 185 190 Pro Thr Ile Ser Leu Phe Ser Glu Glu Gly Leu Lys Gly Lys Pro Val Thr Leu Thr Gly Asp Leu Lys Asp Ser Gln Gly Leu Glu Arg Pro Leu 210 215 220 Gln Val Ala Ser Ala Thr Val Thr Ala Gly Leu Trp Leu Leu Tyr Pro 225 230 235 240 Lys Pro Phe Phe Glu Asp Thr Pro Tyr Ile Leu Glu Pro Gly Glu Tyr 245 250 255 Pro Thr Leu Glu Ala Trp Gly Thr Ser Gly Pro Ser Val Gly Ser Leu 260 . 265 . 270 Lys Pro Met Arg Leu Gly Cys Pro Ser Val Glu Lys Pro Gly Glu Pro 275 280 285 Lys Ala Val Val Tyr Glu Ala Pro Gly Phe Gln Gly Gln Ser Trp Glu 290 295 300

Val Ser Gly Asp Ile Tyr Asn Leu Gln Gln Pro Glu Asp Ser Gln Ser 305 310 315 320 Pro Gln Leu Thr Ser Val Gly Ser Leu Arg Ile Leu Gly Gly Cys Trp 325 330 - 335 Val Gly Tyr Glu Lys Glu Gly Phe Arg Gly His Gln Tyr Leu Leu Glu 340 345 350 Glu Gly Glu Tyr Ala Asp Trp Ser His Trp Gly Gly Tyr Asp Glu Leu 355 360 365 Leu Thr Ser Leu Arg Val Ile Arg Thr Asp Phe Gly Asp Pro Ala Val 370 375 380 Val Leu Phe Glu Asp Met Asp Phe Gln Gly His Arg Val Glu Val Ser 385 390 395 400 390 395 Ser Ala Leu Pro Asp Val Glu Leu Ala Gln His Gly Pro Ser Thr Gln . 410 - 405

```
Ala Ile His Val Leu Ser Gly Val Trp Val Ala Tyr Glu Arg Val Gly
             420
                                    425
                                                            430
Phe Ser Gly Glu Gln Tyr Ile Leu Glu Lys Gly Val Tyr Arg Asn Cys
         435
                              440
Asp Asp Trp Gly Ser Gly Asn Cys Ala Leu Gly Ser Leu Gln Pro Val
450 455 460
Val Gln Val Gly Glu Ser Asp Leu His Phe Val Thr Lys Ile Gln Leu
465 470 475 480
Phe Ser Gly Pro Asn Phe Leu Gly Asp His Ile Ser Phe Glu Asp Asp 485 490 495
Gln Ala Ser Leu Pro Ala Ser Phe His Pro Gln Ser Cys Arg Val His 500 505 510
Gly Gly Ser Trp Val Leu Phe Glu Asp Lys Asn Phe Glu Ala Asp Gln 515 520 525
His Ile Val Ser Glu Gly Glu Phe Pro Thr Leu Thr Asp Met Gly Cys 530 540
Leu Ala Ser Thr Val Leu Gly Ser Leu Arg Lys Val Pro Leu His Phe 545 550 555 560
Ser Glu Pro Ser Leu Ser Leu Phe Gly Leu Glu Cys Phe Glu Gly Lys
565 570 575
Glu Ile Glu Leu Thr Gly Glu Val Arg Ser Leu Gln Ala Glu Gly Phe
580 595 590
Asn Asn His Val Leu Ser Val Arg Val Lys Gly Gly Val Trp Val Val 595 600 605
Cys Glu His Ser Asp Phe Arg Gly Arg Gln Trp Leu Val Gly Ser Cys 610 615 620
                                                  620
Glu Ile Thr Asn Trp Leu Thr Tyr Ser Gly Thr Gln Arg Val Gly Ser 625 630 635 640
Leu Tyr Pro Ile Lys Gln Arg Arg Ala Tyr Phe Arg Leu Trp Asn Ala
645 650 655
Ala Leu Gly Gly Phe Leu Ser Val Pro Asp His Val Glu Asp Met Lys
660 665 670
Ala Gly Arg Val Val Val Ser Glu Pro Arg Ala Gly Gly Ser Cys Ile
675 680 685
Trp Tyr Tyr Glu Asp Gly Leu Leu Lys Asn Gln Met Ala Pro Thr Met : 690 695 700
Ser Leu Gln Val Ile Gly Pro Pro Ser Pro Gly Ser Lys Val Val Leu
705 710 715 720
Trp Ala Glu Ser Arg Leu Pro Arg Gln Thr Trp Ser Ile Asn Glu Leu 725 730 735
Gly His Ile Cys Ser Gln Met Phe Glu Gly Gln Ile Leu Asp Val Lys
740 745 750
Gly Gly Arg Gly Tyr Asp Arg Asp His Val Val Leu Trp Glu Pro Thr
755 760 765
Lys Asp Arg Leu Ser Gln Ile Trp Thr Val His Val Leu
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<210> 669 <211> 70 <212> PRT

<213> Mouse

Arg Val Lys Glu Gly Asp Ile Leu Tyr Ile His Ser Leu Gln Thr Val

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40
        35
                                                    45
Gly Ser Asn His Lys Pro Val Ala Ala Glu His Thr Tyr Trp Ala Trp
    50
                         55
Pro Glu Glu Thr Asp Val
<210> 670
<211> 368
<212> PRT
<213> Mouse
<400> 670
Leu Thr Asn Gly Ser Gln Ala Ser Asp Lys Ser Glu Glu Gly Ser Ala
                 5
 1
                                     10
Asp Thr Ala Asp Pro Gln Glu Asn Pro Leu Gln Pro Val Ser Val Gly 20 25 30
Glu Glu Pro Ser Ile Thr Glu His His Ser Val Gly Glu Gln Ala Trp
35 40 45
Asp Gly Thr Ser Gln Ser Cys Pro Ser Leu Pro Ala Thr Val Ser Phe 50 55 60
His Met Asp Ser Thr Asp Leu Glu Pro Gly Gln Gln Thr Ala Met Lys 65 70 75 80
Ser Cys Ser Arg Asp Asp Val Glu Met Val Glu Glu Phe Asp Glu Leu
85 90 95
Pro Thr Asp Ala Val Arg Arg Ile Arg Arg Glu Leu Val Thr Val Thr 100 105 110
Lys His Ser Pro Glu Gln Arg Gln Asp Pro Leu Cys Ile Ser Ile Thr
115 120 125
Val Cys Thr Val Glu Lys Asp Arg Pro Ala Ala Leu Asp Ser Leu Glu 130 135 140
Glu Pro Leu Pro Gly Met Leu Phe Phe Leu Ser Ser Gly Gln Asp Gln 145 150 155 160
Gln Ala His Pro Gln Leu Arg Glu His Pro Ala Pro Glu Ala Ser Glu
             165
                                   170 175
Ala Ser Gln Pro Gln Asp Ala Ala Glu Gly Ser Ser Ala Gly Glu Glu 180 185 · 190
Lys Asp Ala Ser Val Glu Pro Leu Leu Pro Ala Ala Ser Pro Gly Gly 195 200 205
Ser Thr Ser Gln Val Leu Glu Ala Ala Thr Cys Lys Lys Gln Val Ser 210 \phantom{\bigg|}215\phantom{\bigg|}220\phantom{\bigg|}
Arg Leu Leu Pro Thr Leu Ser Leu Ala Ile Leu Lys Cys Thr Cys Arg 260 265 \cdot 270
Tyr Phe Lys Ser Ile Ile Glu Tyr Tyr Asn Ile Arg Pro Ala Asp Ser 275 280 285
Arg Trp Val Arg Asp Pro Arg Tyr Arg Glu Asp Pro Cys Lys Gln Cys 290 295 300
Lys Lys Lys Tyr Val Lys Gly Asp Val Ser Leu Cys Arg Trp His Pro 305 310 315 320
Lys Pro Tyr Cys Gln Ala Leu Pro Tyr Gly Pro Gly Tyr Trp Met Cys
               • 325
                                      330
Cys Pro Pro Val Ser Glu Gly Leu Phe Cys Cys Lys Leu Gly Leu His
            340
                                  345
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Asp Asn His Trp Leu Pro Ala Cys His Ser Phe Asn Pro Gly Asn Pro

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<211> 293
<212> PRT
<213> Mouse
<400> 671
Thr His Phe Ile His Thr Leu Thr Arg Leu Gln Met Glu Gln Gly Ala
                 5
                                     10
Glu Ser Leu Gly Asp Leu Glu Ser Pro Val Glu Asp Thr Pro Val Glu
         20
Gln Ala Ala Leu Ser Pro Phe Pro Pro Ser Lys Pro Pro Val Ser Ser 35 40 45
Glu Leu Gly Asp Ser Ser Cys Ser Ser Asp Met Thr Asp Ser Ser Thr
                      55
Thr Leu Ser Ser Gly Ser Ser Glu Pro Pro Asn His Pro Ala His Pro 65 70 75 80
Ser Leu Pro Gly Pro Ser Phe Arg Ser Gly Val Asp Glu Asp Ser Leu
85 90 95
Glu Gln Ile Leu Asn Phe Ser Asp Ser Asp Leu Gly Ile Glu Glu Glu 100 105 110
           100
                                105
Glu Glu Glu Gly Gly Gly Val Gly Asn Ser Asp Asn Leu Ser Cys Phe
115 120 125
His Leu Ala Asp Ile Phe Gly Thr Gly Asp Pro Gly Ser Leu Ala Ser
130 135 140
Trp Thr His Ser Gln Ser Gly Ser Ser Leu Ala Ser Gly Ile Leu Asp
145 150 155 160
Glu Asn Ala Asn Leu Asp Ala Ser Cys Phe Leu Asn Ser Gly Leu Gly
165 170 175
Gly Leu Arg Glu Gly Ser Leu Pro Gly Ser Ser Gly Ser Pro Glu Gly 180 185 190
Asp Ala Val Gln Ser Ser Ser Trp Asp Leu Ser Leu Ser Ser Cys Asp 195 200 205
Ser Phe Glu Leu Leu Gln Ala Leu Pro Asp Tyr Ser Leu Gly Pro His 210 215 220
Tyr Thr Ser Arg Arg Val Ser Gly Ser Pro Asp Ser Leu Glu Thr Phe 225 230 240
His Pro Leu Pro Ser Phe Ser Pro Pro Arg Asp Ala Ser Thr Cys Phe
              245
                       250
Leu Glu Ser Leu Val Gly Leu Ser Glu Pro Val Thr Glu Val Leu Ala 260 265 270
Pro Leu Glu Ser Gln Phe Glu Asp Ala Ala Leu Ala Pro Leu Leu
     275
                                                   285
                             280
Glu Pro Val Pro Val
   290
<210> 672
<211> 904
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<213> Mouse
<400> 672
Met Glu Val Asn Cys Leu Thr Leu Lys Asp Leu Ile Ser Pro Arg Gln
                                    10
                                                           15.
Thr Arg Leu Asp Phe Ala Ile Glu Asp Ala Glu Asn Ala Gln Lys Glu
```

```
25
 Asn Ile Phe Val Asp Arg Ser Arg Met Thr Pro Lys Thr Pro Met Lys
        35
                                40
 Asn Glu Pro Ile Asp Leu Ser Lys Gln Arg Ile Phe Thr Pro Asp Arg
    50
                           55
                                                   60
Asn Pro Ile Thr Pro Val Lys Pro Val Asp Arg Gln Pro Gln Val Glu
65 70 75 80
Pro Trp Thr Pro Thr Ala Asn'Leu Lys Met Leu Ile Ser Ala Ala Ser
85 90 95
Pro Asp Ile Arg Asp Arg Glu Lys Lys Lys Glu Leu Phe Arg Pro Ile 100 105 110
Glu Asn Lys Glu Asp Ala Phe Val Asn Ser Leu Gln Leu Asp Val Ala
115 120 125
Gly Asp Gly Ala Val Asp Glu Tyr Glu Lys Gln Arg Pro Ser Arg Lys
130 135 140
Gln Lys Ser Leu Gly Leu Leu Cys Gln Lys Phe Leu Ala Arg Tyr Pro
145 150 150 160
Ser Tyr Pro Leu Ser Thr Glu Lys Thr Thr Ile Ser Leu Asp Glu Val
Ala Val Ser Leu Gly Val Glu Arg Arg Arg Ile Tyr Asp Ile Val Asn 180 185 190
Val Leu Glu Ser Leu His Leu Val Ser Arg Val Ala Lys Asn Gln Tyr
195 200 205
Gly Trp His Gly Arg His Ser Leu Pro Lys Thr Leu Arg Thr Leu Gln 210 215 220
Arg Leu Gly Glu Glu Gln Lys Tyr Glu Glu Gln Met Ala Cys Leu Gln 225 230 235 240
Gln Lys Glu Leu Asp Leu Met Gly Tyr Arg Phe Gly Glu Arg Arg Lys
245 250 255
Asp Gly Ser Pro Asp Pro Arg Asp Pro His Leu Leu Asp Phe Ser Glu 260 265 270
Ala Asp Tyr Pro Ser Ser Ser Ala Asp Ser Arg Lys Asp Lys Ser Leu 275 . 280 285
Arg Ile Met Ser Gln Lys Phe Val Met Leu Phe Leu Val Ser Lys Thr 290 295 300
Lys Ile Val Thr Leu Asp Val Ala Ala Lys Ile Leu Ile Glu Glu Ser 305 310 315 320
Gln Asp Thr Pro Asp His Ser Lys Phe Lys Thr Lys Val Arg Arg Leu 325 330 335
Tyr Asp Ile Ala Asn Val Leu Thr Ser Leu Ala Leu Ile Lys Lys Val
340 345 350
His Val Thr Glu Glu Arg Gly Arg Lys Pro Ala Phe Lys Trp Ile Gly 355 360 365
Pro Val Asp Phe Ser Ser Ile Asp Glu Glu Leu Leu Asp Val Ser Ala
370 375 380
Ser Ile Leu Pro Glu Leu Lys Lys Glu Ala Tyr Gly Gln Ile Arg Val
385 390 . 395 . 400
Cys Ala Lys Glu Arg Leu Val Arg Tyr Gly Ser Phe Asn Thr Val His
405 410 415
Thr Ser Glu Lys Ile Gln Arg Lys Val Ser Ser Glu Pro Ser Ser Pro 420 425 430
Gln Gly Glu Arg Gln Gly Ser Ala Tyr Ser Leu Glu Ile Gly Ser Leu 435 . 445
Ala Ala Ile Tyr Arg Gln Lys Val Glu Asp Asn Ser Gln Glu Glu Ala
450 455 460
Phe Val Ser Asn Thr Ala Val Pro Pro Ala Ser Ile Leu Asp Pro Ala
                      470
                                              475
```

```
Leu Ser Met Asp Ser Glu Tyr Cys Val Lys Pro Leu Ala Gln Pro Val
. 485 490 495
Phe Ser Val Ala Gln Thr Asp Leu Pro Ala Phe Ser Ala Gln Asn Gly 500 505 510
Pro Ser Gly Gln Val Gly Val Pro Val Pro Ser Ala Ala Ser Asp Thr
515 520 525
Glu Asn Leu Lys Pro Ala Leu Leu Ala Gly Gln Pro Leu Val Tyr Val 530 540
Pro Ser Thr Gln Leu Phe Met Leu Tyr Gly Ser Val Gln Glu Gly Leu 545 550 555 560
Ser Pro Glu Ser Arg Ser Glu Glu Asp Gly Gly Gly Ser Asp Val Pro
565 570 575
Ala Asp Leu Ser Val Thr Pro Ser Ala Gln Lys Arg Leu Cys Glu Glu 580 585 590
Arg Asp Pro Gln Glu Glu Glu Asp Glu Pro Ala Met Lys Arg Gln Ser
595 600 605
Gln Glu Phe Glu Asp Ser Pro Leu Ser Leu Val Met Pro Lys Lys Pro 610 615 620 .
Ser Ser Ser Thr Asp Leu Ala Cys Pro Val Thr Met Gly Asn Gly Ser 625 630 635 640
Ser Pro Pro Leu Glu App Ala Cys Val Lys Gly Gln Leu Pro Ala Ala 645 650 655
Glu Glu Val Thr Gly Lys Ala Ala Pro Asn Cys Tyr Val Ala Ser Glu
660 665 670
Cys Gly Asn Pro Ala Arg Asn Pro Asp Thr Glu Lys Pro Ser Asn Glu 675 680 685
Asn Glu Ile Thr Lys Asp Pro Ser Leu Met Gln Tyr Leu Tyr Val Gln
690 695 700
Ser Pro Ala Gly Leu Asn Gly Phe Asn Met Val Leu Pro Gly Thr Gln 705 710 715 720
Thr Pro His Thr Val Ala Pro Ser Pro Ala Gln Leu Pro Ser Phe Gly 725 730 735
Val Pro Cys Met Phe Leu Gln Ser Pro Gly Leu Gly Pro Phe Pro Val
740 745 750
Leu Tyr Ser Pro Ala Ile Pro Gly Pro Ile Ser Ser Ala Pro Gly Thr
755 760 765
His Pro Asn Pro Gly Pro Met Asn Phe Gly Leu Ser Thr Leu Ala Ser 770 775 780
Ala Ser His Leu Leu Ile Ser Pro Ala Ala Met Val Asn Pro Lys Pro 785 790 795 800
Ser Thr Leu Pro Cys Thr Asp Pro Gln Leu Arg Cys Gln Pro Ser Leu
805 810 815
Asn Leu Asn Pro Val Met Pro Gly Ser His Gly Val Ile His Pro Glu
820 825 830
Ser Pro Cys Tyr Val Arg His Pro Val Ser Met Val Lys Ala Glu Gln
835 840 845
Ser Pro Ala Pro Ala Thr Pro Lys Ser Ile Gln Arg Arg His Arg Glu
850 855 860
Thr Phe Phe Lys Thr Pro Gly Ser Leu Gly Asp Pro Val Phe Arg Arg 865 870 880
Lys Glu Arg Asn Gln Ser Arg Asn Thr Ser Ser Ala Gln Arg Arg Leu
                  885
                                          890
                                                               895
Glu Ile Ser Ser Ser Gly Pro Asp
              900
```

<210> 673 <211> 173

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<212> PRT
<213> Mouse
<400> 673
Lys Arg Arg Lys Arg Lys Arg Ser Glu Gly Leu Ser Gln Glu Ala Thr
                                    10
Pro Ser Gln Asp Leu Ile Gln His Ser Cys Ser Pro Val Asp His Ser
           20
                               25
Glu Pro Glu Ala Arg Thr Glu Leu Gln Lys Lys Lys Lys Lys Arg
        35
                            40
                                                45
Arg Lys Arg Lys Pro Glu Pro Gln Gln Asp Glu Glu Ser Lys His Pro
                       55
                                           60
Gly Asp Gln Arg Ser Pro Arg Pro Ser Val Thr Pro Val Pro Ala Leu
65 70 75 75 80
Ser Val Asn Gly His Leu Pro Ser Asp Cys Leu Val Leu Thr Trp Asp
               85
                                   90
                                                       95
Gly Glu Pro Ser Ala Ile Ser Gln Asp Ala Ile Lys Asp Ser Arg Leu
100 105 110
Ala Arg Thr Gln Thr Val Val Asp Asp Trp Asp Glu Glu Phe Asp Arg
115 120 125
Gly Lys Glu Lys Lys Ile Lys Lys Phe Lys Arg Glu Lys Lys Arg Asn
130 135 140
Phe Asn Ala Phe Gln Lys Leu Gln Ser Arg Arg Asn Phe Trp Ser Val
145 150 155 160
Thr His Pro Ala Lys Val Ala Ser Leu Ser Tyr Arg Arg
                165
                                   170
<210> 674
<211> 470
<212> PRT
<213> Mouse
<400> 674
Glu Glu Thr Lys Pro Leu Leu Gly Ser Asp Val Ser Gly Pro Glu Gly
                                  10
Thr Lys Val Met Gly Ala Val Pro Cys Arg Arg Ala Leu Leu Cys 20 25 30
Asn Gly Met Arg Tyr Lys Leu Leu Gln Glu Gly Asp Ile Gln Val Cys
       35
                          40
Val Ile Arg His Pro Arg Thr Phe Leu Ser Lys Ile Leu Thr Ser Lys 50 55 60
Phe Leu Arg Arg Trp Glu Pro His His Leu Thr Leu Ala Asp Asn Ser 65 70 75 80
Leu Ala Ser Ala Thr Pro Ser Gly Tyr Met Glu Asn Ser Val Ser Tyr
               85
                                   90
Tyr Cys Leu Gln Leu Thr Ile Pro Gly Gly Thr Val Leu Leu Gln Ala
115 120 125
Ala Asn Ser Tyr Leu Arg Asp Gln Trp Phe His Ser Leu Gln Trp Lys
130 135 140
Lys Lys Ile Tyr Lys Tyr Lys Lys Val Leu Ser Asn Pro Ser Arg Trp
145 150 155 . 160
```

Glu Val Val Leu Lys Glu Ile Arg Thr Leu Val Asp Met Ala Leu Thr 165 170 175

Ser Pro Leu Gln Asp Asp Ser Ile Asn Gln Ala Pro Leu Glu Ile Val

180

170

185 .

```
Ser Lys Leu Leu Ser Glu Asn Thr Asn Leu Thr Thr Gln Glu His Glu
        195
                                200
Asn Ile Ile Val Ala Ile Ala Pro Leu Leu Glu Asn Asn His Pro Pro
    210
                          215
Pro Asp Leu Cys Glu Phe Phe Cys Lys His Cys Arg Glu Arg Pro Arg 225 230 235 240
Ser Met Val Val Ile Glu Val Phe Thr Pro Val Val Gln Arg Ile Leu 245 250 255
Lys His Asn Met Asp Phe Gly Lys Cys Pro Arg Leu Arg Leu Phe Thr 260 265 270
Glu Glu Tyr Ile Leu Ala Leu Asn Glu Leu Asn Ala Gly Met Glu Val
275 280 285
Val Lys Lys Phe Ile Gln Ser Met His Gly Pro Thr Gly His Cys Pro
290 295 300
His Pro Arg Val Leu Pro Asn Leu Val Ala Val Cys Leu Ala Ala Ile
305 310 315 320
Tyr Ser Cys Tyr Glu Glu Phe Ile Asn Ser Arg Asp Asn Ser Pro Ser 325 330 335
Leu Lys Glu Ile Arg Asn Gly Cys Gln Gln Pro Cys Asp Arg Lys Pro 340 345 350
Thr Leu Pro Leu Arg Leu Leu His Pro Ser Pro Asp Leu Val Ser Gln 355 360 365
Glu Ala Thr Leu Ser Glu Pro Arg Leu Lys Ser Val Val Val Ala Ser 370 375 380
Ser Glu Val His Val Glu Val Glu Arg Thr Ser Thr Ala Lys Pro Ala 385 390 395 400
Leu Thr Ala Ser Thr Gly Asn Asp Ser Glu Pro Asn Leu Ile Asp Cys
405
410
415
Leu Met Val Ser Pro Ala Cys Gly Thr Met Ser Ile Glu Leu Gly Pro
420
425
430
Gin Ala Gly Arg Thr Leu Gly Cys His Val Glu Ile Leu Lys Leu Leu 435 440 445
Ser Asp Tyr Asp Asp Trp Arg Pro Ser Leu Ala Ser Leu Leu Gln Pro 450 455 460
Ile Pro Phe Pro Lys Glu
465
                       470
<210> 675
<211> 319
<212> PRT
<213> Mouse
<400> 675
Phe Ala Arg Thr Leu Pro Trp Ala Ser Val Leu Arg Val Trp Asp Met
                                          10
Phe Phe Cys Glu Gly Val Lys Ile Ile Phe Arg Val Ala Leu Val Leu 20 · 25 -30
Leu Arg His Thr Leu Gly Ser Val Glu Lys Leu Arg Ser Cys Gln Gly
        35
                             40
Met Tyr Glu Thr Met Glu Gln Leu Arg Asn Leu Pro Gln Gln Cys Met 50 55 60
Gln Glu Asp Phe Leu Val His Glu Val Thr Asn Leu Pro Val Thr Glu 65 70 75 80
Ala Trp Ile Glu Arg Glu Asn Ala Ala Gln Leu Lys Lys Trp Arg Glu
85 90 95
                                        90
Thr Arg Gly Glu Leu Gln Tyr Arg Pro Ser Arg Arg Leu His Gly Ser
```

```
Arg Ala Ile His Glu Glu Arg Arg Gln Gln Pro Pro Leu Gly Pro 115 120 125
     115
                                                      125
Ser Ser Ser Leu Leu Ser Leu Pro Ser Leu Lys Ser Arg Gly Ser Arg
                        135
    130
Ala Val Gly Gly Ala Pro Ser Pro Pro Pro Pro Val Arg Arg Ala Ser
145 150 155 160
                    150 155
Ala Gly Pro Val Pro Gly Ala Val Val Ile Ala Glu Gly Leu His Pro
165 170 175
Ser Leu Pro Ser Pro Thr Gly Asn Ser Thr Pro Leu Gly Thr Ser Lys
180 185 190
                                                          190
Glu Ile Arg Arg Gln Glu Lys Glu Arg Gln Lys Gln Glu Lys Asp Arg
195 200 205
Glu Lys Glu Arg Gln Arg Gln Glu Lys Glu Arg Glu Arg Gln Glu Arg
210 215 220

        Ser Gly Arg Ser Gly Lys Arg Ser Lys Arg Arg Arg Asn Ser Arg Ser Arg

        225
        230
        235
        240

Arg Arg Ser Gly Arg Ser Trp Arg Arg Lys Ala Lys Ala Gly Asn Cys
245 250 255
Pro Cys Val Glu Gly Gln Met Gly Pro Arg His Pro Met Met Val Gly
260 265 270
Thr Gly Gln Gln Leu Arg Pro Gly Arg Met Leu Thr Phe Asp Leu Trp 275 280 285
Leu Asp Leu Asp Gly Met Ala Leu Leu Leu Pro Leu Ile Glu Ser Ser 290 295 300
Pro Gly Arg Leu Ser Gln Leu Pro Leu Ala Gly Ser Ser Phe Phe
305
                      310
                                              315
<210> 676
<211> 94
<212> PRT
<213> Mouse
<400> 676
Met Phe Ser Glu Lys Lys His Phe Leu His Thr Ile Gln Asn Pro Glu
                                       10
Ser Glu Lys Glu Arg Arg Arg Arg Arg Arg Arg Arg Arg Ser Arg Arg 20 25 30
Arg Glu Arg Lys Lys Glu Arg Lys Glu Arg Lys Glu Arg Lys 35 40 45
Gln Ala Ser Leu Pro Ser Val Lys Arg Glu Arg Ala Trp His Gly Glu
                          55
Gln Thr Gln Gly Ser Leu Ser Thr Val Arg Gln Glu Ser Ser Pro Gly 65 70 75 80
His Arg Ala Lys Val Ile Ala Asp Leu Gly Lys Asn Asp Gln
                  85
                                         90
<210> 677
<211> 137
<212> PRT
<213> Mouse
<400> 677
Val Arg Trp Lys Met Arg Arg Ser Leu Arg Ala Gly Arg Arg Arg Gln 1 5 10 15
Thr Ala Gly Arg Lys Ser Lys Ser Pro Pro Lys Val Pro Ile Val Ile 20 25 \cdot 30
Gln Asp Asp Ser Leu Pro Thr Gly Pro Pro Pro Gln Ile Arg Ile Leu
```

```
Lys Arg Pro Thr Ser Asn Gly Val Val Ser Ser Pro Asn Ser Thr Ser 50 55 60
Arg Pro Ala Leu Pro Val Lys Ser Leu Ala Gln Arg Glu Ala Glu Tyr 65 70 75 80
Ala Glu Ala Arg Arg Ile Leu Gly Ser Ala Ser Pro Glu Glu Glu 85 90 95
Gln Glu Lys Pro Ile Leu Asp'Arg Pro Thr Arg Ile Ser Gln Pro Glu
100 105 110
Asp Ser Arg Gln Pro Ser Asn Val Ile Arg Gln Pro Leu Gly Pro Asp
115 120 125
Gly Ser Gln Gly Phe Lys Gln Arg Arg
    130
<210> 678
<211> 380
<212> PRT
<213> Mouse
<400> 678
Glu Thr Thr Ile Thr Thr Asp Ser Arg Asp Tyr Gln Met Ala Lys Gly 1 5 10 15
Lys Arg Lys Asn Leu Thr Asn Arg Asn Gln Asp His Ser Leu Ser Ser 20 25 30 .
Glu Pro Ser Thr Pro Thr Ser Ala Ser Pro Gly Tyr Pro Asp Thr Pro 35 40 45
Glu Lys Gln Asp Ser Asn Leu Lys Ser Tyr Leu Met Met Leu Val Glu
50 55 60
Asp Ile Lys Lys Gly Phe Asn Asn Ser Leu Lys Glu Val Lys Glu Asn 65 70 75 80
Thr Ala Lys Glu Val Glu Val Leu Lys Glu Ile Gln Glu Asn Thr Thr 85 90 95
Lys Gln Val Met Glu Leu Asn Lys Ile Ile Gln Asp Leu Lys Arg Glu
100 105 110
Val Glu Thr Lys Lys Thr Gln Asn Glu Thr Thr Leu Glu Ile Glu Thr
115 120 125
Leu Val Lys Lys Ser Gly Thr Ile Asp Val Ser Ile Ser Asn Arg Ile
130 135 140
Gln Glu Met Glu Glu Arg Ile Ser Gly Ala Glu Asp Ser Ile Glu Asn
145 150 155 160
Ile Gly Thr Thr Thr Lys Glu Asn Ala Lys Arg Lys Lys Ile Leu Thr 165 170 175
Gln Asn Ile Gln Lys Ile Gln Asp Lys Met Arg Arg Pro Asn Leu Trp
180 185 190
Ile Ile Gly Val Asp Glu Asp Glu Asp Ser Gln Leu Lys Gly Pro Ala
195 200 205
Asn Ile Phe Asn Lys Phe Ile Glu Glu Asn Phe Pro Asn Leu Lys Lys 210 215 220
Glu Met Ser Met Asn Arg Gln Glu Ala Tyr Arg Thr Pro Asn Arg Leu
225 230 235 240
Asp Gln Lys Arg Asn Ser Ser Leu His Ile Ile Arg Thr Thr Asn 245 250 255
Val Thr Tyr Lys Gly Arg Pro Ile Arg Ile Thr Pro Asp Phe Ser Pro
                           280
Glu Thr Met Lys Ala Arg Arg Ser Trp Thr Asp Val Met Gln Thr Leu
```

295

Arg Glu His Lys Cys Gln Pro Arg Leu Leu Tyr Pro Ala Lys Leu Ser 305 310 315 320 Ile Thr Ile Asp Gly Glu Thr Lys Val Phe His Asp Lys Thr Lys Phe 325 330 335

```
Thr Gln Tyr Leu Ser Met Asn Pro Gly Leu Gln Arg Ile Ile Lys Gly 340 345 350
Lys His Gln His Lys Asp Gly Asn Tyr Thr Leu Glu Lys Ala Arg Lys
355 360 365
Arg Ser Phe Asn Lys Pro Lys Arg Arg Gln Pro Lys
<210> 679
<211> 210
<212> PRT
<213> Mouse
<400> 679
Tyr Gly Thr His Asn His Cys Trp Leu Ser Leu His Arg Gly Phe Ile 1 5 10 15
Trp Ser Phe Leu Gly Pro Ala Ala Ala Ile Ile Leu Ile Asn Leu Val
20 25 30
Phe Tyr Phe Leu Ile Ile Trp Ile Leu Arg Ser Lys Leu Ser Ser Leu 35 40 45
Asn Lys Glu Val Ser Thr Leu Gln Asp Thr Lys Val Met Thr Phe Lys 50 55 60
Ala Ile Val Gln Leu Phe Val Leu Gly Cys Ser Trp Gly Ile Gly Leu
65 70 75 80
Phe Ile Phe Ile Glu Val Gly Lys Thr Val Arg Leu Ile Val Ala Tyr 85 90 95
Leu Phe Thr Ile Ile Asn Val Leu Gln Gly Val Leu Ile Phe Met Val 100 105 110
His Cys Leu Leu Asn Arg Gln Val Arg Met Glu Tyr Lys Lys Trp Phe
115 120 125
His Arg Leu Arg Lys Glu Val Glu Ser Glu Ser Thr Glu Val Ser His
130 135 140
Ser Thr Thr His Thr Lys Met Gly Leu Ser Leu Asn Leu Glu Asn Phe
145 150 155 160
Cys Pro Thr Gly Asn Leu His Asp Pro Ser Asp Ser Ile Leu Pro Ser
165 170 175
Thr Glu Val Ala Gly Val Tyr Leu Ser Thr Pro Arg Ser His Met Gly 180 185 190
                                            190
Ala Glu Asp Val Asn Ser Gly Thr His Ala Tyr Trp Ser Arg Thr Ile
  195
                              200
                                                    205
Ser Asp
    210
<210> 680
<211> 373
<212> PRT
<213> Mouse
<400> 680
Met Lys Glu Tyr Val Met Leu Leu Leu Leu Ala Val Cys Ser Ala Lys
                 5
                                    10
Pro Phe Phe Ser Pro Ser His Thr Ala Leu Lys Asn Met Met Leu Lys
                                  25.
                                                         30
```

```
40
Leu Phe Pro Thr Lys Glu Pro Val Asn Pro Phe Phe Pro Phe Asp Leu
Phe Pro Thr Cys Pro Phe Gly Cys Gln Cys Tyr Ser Arg Val Val His 65 70 75 80
Cys Ser Asp Leu Gly Leu Thr Ser Val Pro Asn Asn Ile Pro Phe Asp
85 90 95
Thr Arg Met Val Asp Leu Gln Asn Asn Lys Ile Lys Glu Ile Lys Glu 100 105 110
Asn Asp Phe Lys Gly Leu Thr Ser Leu Tyr Ala Leu Ile Leu Asn Asn
115 120 125
Asn Lys Leu Thr Lys Ile His Pro Lys Thr Phe Leu Thr Thr Lys Lys
130 135 140
Leu Arg Arg Leu Tyr Leu Ser His Asn Gln Leu Ser Glu Ile Pro Leu
145 150 155 160
Asn Leu Pro Lys Ser Leu Ala Glu Leu Arg Ile His Asp Asn Lys Val
165 170 175
Lys Lys Ile Gln Lys Asp Thr Phe Lys Gly Met Asn Ala Leu His Val
180 185 190
Leu Glu Met Ser Ala Asn Pro Leu Glu Asn Asn Gly Ile Glu Pro Gly 195 200 205
Ala Phe Glu Gly Val Thr Val Phe His Ile Arg Ile Ala Glu Ala Lys 210 215 220
Leu Thr Ser Ile Pro Lys Gly Leu Pro Pro Thr Leu Leu Glu Leu His 225 230 235 240
Leu Asp Phe Asn Lys Ile Ser Thr Val Glu Leu Glu Asp Leu Lys Arg 245 250 255
Tyr Arg Glu Leu Gln Arg Leu Gly Leu Gly Asn Asn Arg Ile Thr Asp 260 265 270
Ile Glu Asn Gly Thr Phe Ala Asn Ile Pro Arg Val Arg Glu Ile His 275 280 285
Leu Glu His Asn Lys Leu Lys Lys Ile Pro Ser Gly Leu Gln Glu Leu 290 295 300
Lys Tyr Leu Gln Ile Ile Phe Leu His Tyr Asn Ser Ile Ala Lys Val
305 310 315 320
Gly Val Asn Asp Phe Cys Pro Thr Val Pro Lys Met Lys Lys Ser Leu 325 330 . 335
Tyr Ser Ala Ile Ser Leu Phe Asn Asn Pro Met Lys Tyr Trp Glu Ile 340 345 350
Gln Pro Ala Thr Phe Arg Cys Val Leu Gly Arg Met Ser Val Gln Leu
355 360 365
                              360
Gly Asn Val Gly Lys
    370
<210> 681
<211> 466
<212> PRT
<213> Mouse
<400> 681
Met Trp Gly Cys Trp Leu Gly Leu Leu Leu Leu Leu Leu Ala Gly Gln
1 10 15
                                      10
Ala Ala Leu Glu Ala Arg Arg Ser Arg Trp Arg Arg Glu Leu Ala Pro 20 25 30
Gly Leu His Leu Arg Gly Ile Arg Asp Ala Gly Gly Arg Tyr Cys Gln
      · 35
                               40
```

```
Glu Gln Asp Met Cys Cys Arg Gly Arg Ala Asp Glu Cys Ala Leu Pro
Tyr Leu Gly Ala Thr Cys Tyr Cys Asp Leu Phe Cys Asn Arg Thr Val
65 70 75 80
65
Ser Asp Cys Cys Pro Asp Phe Trp Asp Phe Cys Leu Gly Ile Pro Pro 85 90 95
                                        90
Pro Phe Pro Pro Val Gln Gly Cys Met His Gly Gly Arg Ile Tyr Pro
100 105 110
Val Phe Gly Thr Tyr Trp Asp Asn Cys Asn Arg Cys Thr Cys His Glu
115 120 125
Gly Gly His Trp Glu Cys Asp Gln Glu Pro Cys Leu Val Asp Pro Asp
130 135 140
Met Ile Lys Ala Ile Asn Arg Gly Asn Tyr Gly Trp Gln Ala Gly Asn 145 150 155 160
His Ser Ala Phe Trp Gly Met Thr Leu Asp Glu Gly Ile Arg Tyr Arg
165 170 175
Leu Gly Thr Ile Arg Pro Ser Ser Thr Val Met Asn Met Asn Glu Ile
180 185 190
Tyr Thr Val Leu Gly Gln Gly Glu Val Leu Pro Thr Ala Phe Glu Ala 195 200 205
Ser Glu Lys Trp Pro Asn Leu Ile His Glu Pro Leu Asp Gln Gly Asn 210 215 220
Cys Ala Gly Ser Trp Ala Phe Ser Thr Ala Ala Val Ala Ser Asp Arg
225 230 235 240
Val Ser Ile His Ser Leu Gly His Met Thr Pro Ile Leu Ser Pro Gln 245 250 255
Asn Leu Leu Ser Cys Asp Thr His His Gln Gln Gly Cys Arg Gly Gly 260 265 270
Arg Leu Asp Gly Ala Trp Trp Phe Leu Arg Arg Arg Gly Val Val Ser 275 280 285
Asp Asn Cys Tyr Pro Phe Ser Gly Arg Glu Gln Asn Glu Ala Ser Pro 290 295 300
Thr Pro Arg Cys Met Met His Ser Arg Ala Met Gly Arg Gly Lys Arg 305 310 315 320
Gln Ala Thr Ser Arg Cys Pro Asn Gly Gln Val Asp Ser Asn Asp Ile
. 325 330 335
Tyr Gln Val Thr Pro Ala Tyr Arg Leu Gly Ser Asp Glu Lys Glu Ile
340
345
350

Met Lys Glu Leu Met Glu Asn Gly Pro Val Gln Ala Leu Met Glu Val
355
360
365
His Glu Asp Phe Phe Leu Tyr Gln Arg Gly Ile Tyr Ser His Thr Pro
370 375 380
Val Ser Gln Gly Arg Pro Glu Gln Tyr Arg Arg His Gly Thr His Ser
385 390 395 400
Val Lys Ile Thr Gly Trp Gly Glu Glu Thr Leu Pro Asp Gly Arg Thr 405 . 410 415 .
Ile Lys Tyr Trp Thr Ala Ala Asn Ser Trp Gly Pro Trp Trp Gly Glu
420 425 430
Arg Gly His Phe Arg Ile Val Arg Gly Thr Asn Glu Cys Asp Ile Glu
435 440 445
Thr Phe Val Leu Gly Val Trp Gly Arg Val Gly Met Glu Asp Met Gly
    450
                             455
His His
465
```

<210> 682 <211> 210

<212> PRT

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<213> Mouse
<400> 682
Met Arg Leu Arg Leu Leu Ala Leu Ala Ala Ala Val Leu Leu Gly Pro
                 -5
                                     10
Ala Pro Glu Val Cys Gly Ala Leu Asn Val Thr Val Ser Pro Gly Pro
          20
                                25
                                                    30
Val Val Asp Tyr Leu Glu Glu Glu Asn Ala Thr Leu Leu Cys His Val 35 40 45
Ser Gln Lys Arg Arg Lys Asp Ser Leu Leu Ala Val Arg Trp Phe Phe 50 55 60
Ala Pro Asp Gly Ser Gln Glu Ala Leu Met Val Lys Met Thr Lys Leu 65 70 75 80
Arg Ile Ile Gln Tyr Tyr Gly Asn Phe Ser Arg Thr Ala Asn Gln Gln 85 90 95
Arg Leu Arg Leu Leu Glu Glu Arg Arg Gly Val Leu Tyr Arg Leu Ser
           100
                               105
Val Leu Thr Leu Arg Pro Thr Asp Gln Gly Gln Tyr Val Cys Lys Val
115 120 125
                                                125
Gln Glu Ile Ser Lys His Arg Asn Lys Trp Thr Ala Trp Ser Asn Gly
130 135 140
Ser Ser Ala Thr Glu Met Arg Val Ile Ser Leu Lys Ala Gly Glu Asp
145 150 155 160
Ser Ser Phe Glu Lys Lys Lys Val Thr Trp Ala Phe Phe Glu Asp Leu
165 170 175
Tyr Val Tyr Ala Val Leu Val Cys Cys Val Gly Ile Leu Ser Val Leu
           180
                                185
                                                  190
Leu Phe Thr Leu Val Ile Ala Cys Ser Leu Cys Phe Thr Arg Gly Asn
       195
                            200
Gln Glu
    210
<210> 683
<211> 255
<212> PRT
<213> Mouse
Met Asp Phe Trp Leu Trp Leu Leu Tyr Phe Leu Pro Val Ser Gly Ala
                                     10
Leu Arg Val Leu Pro Glu Val Gln Leu Asn Val Glu Trp Gly Gly Ser 20 25 30
Ile Ile Ile Glu Cys Pro Leu Pro Gln Leu His Val Arg Met Tyr Leu
       35
                            40
                                                 45
Cys Arg Gln Met Ala Lys Pro Gly Ile Cys Ser Thr Val Val Ser Asn.
   50
                       55
Thr Phe Val Lys Lys Glu Tyr Glu Arg Arg Val Thr Leu Thr Pro Cys 65 70 75 80
Leu Asp Lys Lys Leu Phe Leu Val Glu Met Thr Gln Leu Thr Glu Asn
               85
                                    90
Asp Asp Gly Ile Tyr Ala Cys Gly Val Gly Met Lys Thr Asp Lys Gly 100 105 110
Lys Thr Gln Lys Ile Thr Leu Asn Val His Asn Glu Tyr Pro Glu Pro
                                                 125
                            120
Phe Trp Glu Asp Glu Trp Thr Ser Glu Arg Pro Arg Trp Leu His Arg
                         135
                                             140
```

```
Phe Leu Gln His Gln Met Pro Trp Leu His Gly Ser Glu His Pro Ser
                   150
                                        155
                                                             160
Ser Ser Gly Val Ile Ala Lys Val Thr Thr Pro Ala Ser Lys Thr Glu
                                  170
Ala Pro Pro Val His Gln Pro Ser Ser Ile Thr Ser Val Thr Gln His
180 185 190
Pro Arg Val Tyr Arg Ala Phe Ser Val Ser Ala Thr Lys Ser Pro Ala
195 200 205
Leu Leu Pro Ala Thr Thr Ala Ser Lys Thr Ser Thr Gln Gln Ala Ile
210 215 220
Arg Pro Leu Glu Ala Ser Tyr Ser His His Thr Arg Leu His Glu Gln 225 230 235 240
Arg Thr Arg His His Gly Pro His Tyr Gly Arg Glu Asp Arg Gly
                245
                                    250
<210> 684
<211> 228
<212> PRT
<213> Mouse
<400> 684
Met Lys Ala Leu Arg Ala Val Leu Leu Ile Leu Leu Leu Ser Gly Gln 1 5 10 15
Pro Gly Ser Gly Trp Ala Gln Glu Asp Gly Asp Ala Asp Pro Glu Pro 20 25 30
Thr Asn Met Ile Pro Gly Ser Arg Asp Arg Ala Pro Leu Gln Cys Tyr 50 55 60
Phe Cys Gln Val Leu His Ser Gly Glu Ser Cys Asn Gln Thr Gln Ser 65 70 75 80
Cys Ser Ser Ser Lys Pro Phe Cys IIe Thr Leu Val Ser His Ser Gly 85 90 95
Thr Asp Lys Gly Tyr Leu Thr Thr Tyr Ser Met Trp Cys Thr Asp Thr
100 105 110
                                                   110
Cys Gln Pro Ile Ile Lys Thr Val Gly Gly Thr Gln Met Thr Gln Thr
115 120 125
Cys Cys Gln Ser Thr Leu Cys Asn Ile Pro Pro Trp Gln Asn Pro Gln 130 135 140
Thr Arg His Pro Gln Gly Gly Lys Phe Ser His Pro Gln Val Val Lys
165 170 175
Ala Ala His Pro Gln Ser Asp Gly Ala Asn Leu Pro Lys Ser Gly Lys
180 185 190
Ala Asn Gln Pro Gln Gly Ser Gly Ala Gly Tyr Pro Ser Gly Trp Thr,
Lys Phe Gly Asn Ile Ala Leu Leu Leu Ser Phe Phe Thr Cys Leu Trp
  210
                       215
Ala Ser Gly Ala
225
<210> 685
<211> 242
<212> PRT
<213> Mouse
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<400> 685 Met Ala Ser Gly Trp Phe Tyr Leu Ser Cys Met Val Leu Gly Ser Leu 1 5 10 15 Gly Ser Met Cys Ile Leu Phe Thr Ala Tyr Trp Met Gln Tyr Trp Arg 20 25 30Gly Gly Phe Ala Trp Asp Gly Thr Val Leu Met Phe Asn Trp His Pro 35 40 45 Val Leu Met Val Ala Gly Met Val Val Leu Tyr Gly Ala Ala Ser Leu 50 55 60 Val Tyr Arg Leu Pro Ser Ser Trp Val Gly Pro Arg Leu Pro Trp Lys 65 70 75 80 Val Leu His Ala Ala Leu His Leu Leu Ala Phe Thr Cys Thr Val Val 85 90 95 85 . Gly Leu Ile Ala Val Phe Arg Phe His Asn His Ser Arg Ile Ala His 100 105 110 Leu Tyr Ser Leu His Ser Trp Leu Gly Ile Thr Thr Val Val Leu Phe 115 120 125 Ala Cys Gln Trp Phe Leu Gly Phe Ala Val Phe Leu Leu Pro Trp Ala 130 135 140 Ser Gln Trp Leu Arg Ser Leu Leu Lys Pro Leu His Val Phe Phe Gly 145 150 155 160 Ala Cys Ile Leu Ser Leu Ser Ile Thr Ser Val Ile Ser Gly Ile Asn 165 170 Glu Lys Leu Phe Phe Val Leu Lys Asn Ala Thr Lys Pro Tyr Ser Ser 180 185 190 Leu Pro Gly Glu Ala Val Phe Ala Asn Ser Thr Gly Leu Leu Val Val 195 200 205 Ala Phe Gly Leu Leu Val Leu Tyr Val Leu Leu Ala Ser Ser Trp Lys 215 220 Arg Pro Asp Pro Gly Ala Leu Thr Asp Arg Gln Pro Leu Leu His Asp 225 230 235 Arg Glu

<210> 686 <211> 188 <212> PRT <213> Mouse

```
130
Tyr Leu Gly Glu Phe Gly Glu Asp Gln Ile Tyr Glu Ala Tyr Arg Gln 145 150 155 160
Gly Gln Ala Asn Leu Glu Ala Leu Leu Cys Gly Gly Thr His Gly Pro
165 170 175
Cys Ser Gln Glu Ile Leu Ala Gln Arg Glu Glu Leu
            180 185
<210> 687
<211> 247
<212> PRT
<213> Mouse
<400> 687
Met Ile Pro Gln Val Val Thr Ser Glu Thr Val Thr Val Ile Ser Pro
                 5
                                  10
Asn Gly Ile Ser Phe Pro Gln Thr Asp Lys Pro Gln Pro Ser His Gln
        20 25
                                                      30
Ser Gln Asp Arg Leu Lys Lys His Leu Lys Ala Glu Ile Lys Val Met 35 40 45
                                                 45
Ala Ile Gln Ile Met Cys Ala Val Met Val Leu Ser Leu Gly Ile 50 0 0 0 0
Ile Leu Ala Ser Val Pro Ser Asn Leu His Phe Thr Ser Val Phe Ser 65 70 80
Ile Leu Leu Glu Ser Gly Tyr Pro Phe Val Gly Ala Leu Phe Phe Ala 85 90 95
Ile Ser Gly Ile Leu Ser Ile Val Thr Glu Lys Lys Met Thr Lys Pro 100 105 110
Leu Val His Ser Ser Leu Ala Leu Ser Ile Leu Ser Val Leu Ser Ala
115 120 125
Leu Thr Gly Ile Ala Ile Leu Ser Val Ser Leu Ala Ala Leu Glu Pro
130 135 140
Ala Leu Gln Gln Cys Lys Leu Ala Phe Thr Gln Leu Asp Thr Thr Gln 145 150 150 160
Asp Ala Tyr His Phe Phe Ser Pro Glu Pro Leu Asn Ser Cys Phe Val
. 165 170 175
Ala Lys Ala Ala Leu Thr Gly Val Phe Ser Leu Met Leu Ile Ser Ser
180 185 190
Val Leu Glu Leu Gly Leu Ala Val Leu Thr Ala Thr Leu Trp Trp Lys
195 200 205
Gln Ser Ser Ser Ala Phe Ser Gly Asn Val Ile Phe Leu Ser Gln Asn 210 215 220
Ser Lys Asn Lys Ser Ser Val Ser Ser Glu Ser Leu Cys Asn Pro Thr
225 230 235 240
                                       235
Tyr Glu Asn Ile Leu Thr Ser
                 245
<210> 688
<211> 121
<212> PRT
<213> Mouse
<400> 688
Tyr Gln Arg Arg Ser Lys Thr Leu Glu Glu Leu Ala Asn Asp Ile Lys
                                      10
                                                            15
Glu Asp Ala Ile Ala Pro Arg Thr Leu Pro Trp Thr Lys Gly Ser Asp
```

25.

```
Thr Tle Ser Lys Asn Gly Thr Leu Ser Ser Val Thr Ser Ala Arg Ala
        35
                              40
Leu Arg Pro Pro Lys Ala Ala Pro Pro Arg Pro Gly Thr Phe Thr Pro
    50
                55
Thr Pro Ser Val Ser Ser Gln Ala Leu Ser Ser Pro Arg Leu Pro Arg
      70
                             75
Val Asp Glu Pro Pro Pro Gln Ala Val Ser Leu Thr Pro Gly Gly Val
85 90 95
Ser Ser Ser Ala Leu Ser Arg Met Gly Ala Val Pro Val Met Val Pro
100 105 110
Ala Gln Ser Gln Ala Gly Ser Leu Val
       115
<210> 689
<211> 255
<212> PRT
<213> Mouse
<400> 689
Pro Ala Phe Ser Ser Ala Ala Met Ser Trp Ser Pro Ile Leu Pro Phe
                 5
                                     10
Leu Ser Leu Leu Leu Leu beu Phe Pro Leu Glu Val Pro Arg Ala Ala
       20
                              25
                                                      30
Thr Ala Ser Leu Ser Gln Ala Ser Ser Glu Gly Thr Thr Thr Cys Lys 35 40 45
Val His Asp Val Cys Leu Leu Gly Pro Arg Pro Leu Pro Pro Ser Pro 50 55 60
Pro Val Arg Val Ser Leu Tyr Tyr Glu Ser Leu Cys Gly Ala Cys Arg 65 70 75 80
Tyr Phe Leu Val Arg Asp Leu Phe Pro Thr Trp Leu Met Val Met Glu 85 90 95
Ile Met Asn Ile Thr Leu Val Pro Tyr Gly Asn Ala Gln Glu Arg Asn
100 105 110
Val Ser Gly Thr Trp Glu Phe Thr Cys Gln His Gly Glu Leu Glu Cys
115 120 125
Arg Leu Asn Met Val Glu Ala Cys Leu Leu Asp Lys Leu Glu Lys Glu
130 135 140
Ala Ala Phe Leu Thr Ile Val Cys Met Glu Glu Met Asp Asp Met Glu
145 150 155 160
Lys Lys Leu Gly Pro Cys Leu Gln Val Tyr Ala Pro Glu Val Ser Pro
165 170 175
Glu Ser Ile Met Glu Cys Ala Thr Gly Lys Arg Gly Thr Gln Leu Met
180 185 190
His Glu Asn Ala Gln Leu Thr Asp Ala Leu His Pro Pro His Glu Tyr
195 200 205
Val Pro Trp Val Leu Val Asn Glu Lys Pro Leu Lys Asp Pro Ser Glu 210 215 220
Leu Leu Ser Ile Val Cys Gln Leu Asp Gln Gly Thr Glu Lys Pro Asp
225 230 235 240
```

Ile Cys Ser Ser Ile Ala Asp Ser Pro Arg Lys Val Cys Tyr Lys

245

<210> 690

<211> 255

<212> PRT

<213> Mouse

```
<400> 690
Met Val Trp Thr Gln Asp Arg Leu His Asp Arg Gln Arg Val Val His
                                      10
Trp Asp Leu Ser Gly Asp Pro Gly Ser Gln Arg Arg Arg Leu Val Asp 20 25 30
Met Tyr Ser Ala Gly Glu Gln Arg Val Tyr Glu Pro Arg Asp Arg Asp 35 40 45
Arg Leu Leu Ser Pro Ser`Ala Phe His Asp Gly Asn Phe Ser Leu 50 55 60
Leu Ile Arg Ala Val Glu Arg Gly Asp Glu Gly Val Tyr Thr Cys Asn 65 70 75 80
Leu His His His Tyr Cys His Leu Asp Glu Ser Leu Ala Val Arg Leu 85 90 95
Glu Val Thr Asp Asp Pro Leu Leu Ser Arg Ala Tyr Trp Asp Gly Glu 100 105 110
Lys Glu Val Leu Val Val Ala His Gly Ala Pro Ala Leu Met Thr Cys
Ile Asn Arg Ala His Val Trp Thr Asp Arg His Leu Glu Glu Ala Gln 130 . 135 140
Gln Val Val His Trp Asp Arg Gln Leu Pro Gly Val Ser His Asp Arg
145 150 155 160
Ala Asp Arg Leu Leu Asp Leu Tyr Ala Ser Gly Glu Arg Arg Ala Tyr
165 170 175
                                      170
Gly Pro Pro Phe Leu Arg Asp Arg Val Ser Val Asn Thr Asn Ala Phe 180 185 190
Ala Arg Gly Asp Phe Ser Leu Arg Ile Asp Glu Leu Glu Arg Ala Asp
195 200 205
Glu Gly Ile Tyr Ser Cys His Leu His His His Tyr Cys Gly Leu His 210 215 220
Glu Arg Arg Val Phe His Leu Gln Val Thr Glu Pro Ala Phe Glu Pro
                   230
                                          235
Pro Ala Arg Ala Ser Pro Gly Asn Gly Ser Gly His Ser Ser Ala
               245
                                       250
```

<210> 691 <211> 255 <212> PRT

<213> Mouse

<400> 691

 Met
 Lys
 Leu
 Lys
 Gln
 Arg
 Val
 Leu
 Val
 Ile
 Ile
 Leu
 Leu
 Val
 Ile
 Ile
 Leu
 Leu
 Leu
 Ile
 Ile
 Leu
 Leu
 Ile
 Leu
 Ile
 Leu
 Ile
 Leu
 Ile
 Leu
 Ile
 Leu
 Ile
 th

```
130
                            135
Asn Ala Glu Val Ala Ala Phe His Leu Asp Arg Ile Leu Gly Phe Arg
145 150 155 160
Arg Ala Pro Leu Val Val Gly Arg Tyr Val Asn Leu Arg Thr Glu Val
Lys Pro Val Ala Thr Glu Gln Leu Leu Ser Thr Phe Leu Thr Val Gly
180 185 190
Asn Asn Thr Cys Phe Tyr Gly Lys Cys Tyr Tyr Cys Arg Glu Thr Glu
195 200 205
Pro Ala Cys Ala Asp Gly Asp Met Met Glu Gly Ser Val Thr Leu Trp
210 215 220
Leu Pro Asp Val Trp Pro Leu Gln Lys His Arg His Pro Trp Gly Arg 225 230 235 240
Thr Tyr Arg Glu Gly Lys Leu Ala Arg Trp Glu Tyr Asp Glu Ser
245 250 255
<210> 692
<211> 255
 <212> PRT
 <213> Mouse
 <400> 692
Met Gln Thr Met Trp Gly Ser Gly Glu Leu Leu Val Ala Trp Phe Leu 1 5 10 10 15
Val Leu Ala Ala Asp Gly Thr Thr Glu His Val Tyr Arg Pro Ser Arg
20 25 30
Arg Val Cys Thr Val Gly Ile Ser Gly Gly Ser Ile Ser Glu Thr Phe
Val Gln Arg Val Tyr Gln Pro Tyr Leu Thr Thr Cys Asp Gly His Arg 50 55 60
Ala Cys Ser Thr Tyr Arg Thr Ile Tyr Arg Thr Ala Tyr Arg Arg Ser 65 70 75 80
Pro Gly Val Thr Pro Ala Arg Pro Arg Tyr Ala Cys Cys Pro Gly Trp
85 90 95
Lys Arg Thr Ser Gly Leu Pro Gly Ala Cys Gly Ala Ala Ile Cys Gln
100 105 110
Pro Pro Cys Gly Asn Gly Gly Ser Cys Ile Arg Pro Gly His Cys Arg
Cys Pro Val Gly Trp Gln Gly Asp Thr Cys Gln Thr Asp Val Asp Glu
130 135 140
Cys Ser Thr Gly Glu Ala Ser Cys Pro Gln Arg Cys Val Asn Thr Val
145 150 155 160
Gly Ser Tyr Trp Cys Gln Gly Trp Glu Gly Gln Ser Pro Ser Ala Asp
165 170 175
Gly Thr Arg Cys Leu Ser Lys Glu Gly Pro Ser Pro Val Ala Pro Asn
180 185 190
Pro Thr Ala Gly Val Asp Ser Met Ala Arg Glu Glu Val·Tyr Arg Leu
195 . 200 205
Gln Ala Arg Val Asp Val Leu Glu Gln Lys Leu Gln Leu Val Leu Ala
210 215 220
Pro Leu His Ser Leu Ala Ser Arg Ser Thr Glu His Gly Leu Gln Asp
225 230 235 240
Pro Gly Ser Leu Leu Ala His Ser Phe Gln Gln Leu Asp Arg Ile
                 245
<210> 693
```

<211> 255

<212> PRT <213> Mouse <400> 693 Met Arg Leu Thr Val Gly Ala Leu Leu Ala Cys Ala Ala Leu Gly Leu 5 10 Cys Leu Ala Val Pro Asp Lys Thr Val Lys Trp Cys Ala Val Ser Glu 20 25 30 His Glu Asn Thr Lys Cys Ile Ser Phe Arg Asp His Met Lys Thr Val 35 40 45 Leu Pro Pro Asp Gly Pro Arg Leu Ala Cys Val Lys Lys Thr Ser Tyr 50 55 60 Pro Asp Cys Ile Lys Ala Ile Ser Ala Ser Glu Ala Asp Ala Met Thr 65 70 75 80 Leu Asp Gly Gly Trp Val Tyr Asp Ala Gly Leu Thr Pro Asn Asn Leu 85 90 95 Lys Pro Val Ala Ala Glu Phe Tyr Gly Ser Val Glu His Pro Gln Thr 100 105 110Tyr Tyr Tyr Ala Val Ala Val Val Lys Lys Gly Thr Asp Phe Gln Leu 115 120 125 Asn Gln Leu Glu Gly Lys Lys Ser Cys His Thr Gly Leu Gly Arg Ser 130 135 140 Ala Gly Trp Val Ile Pro Ile Gly Leu Leu Phe Cys Lys Leu Ser Glu 145 155 160 Pro Arg Ser Pro Leu Glu Lys Ala Val Ser Ser Phe Phe Ser Gly Ser 165 170 175 Cys Val Pro Cys Ala Asp Pro Val Ala Phe Pro Lys Leu Cys Gln Leu 180 185 190 Cys Pro Gly Cys Gly Cys Ser Ser Thr Gln Pro Phe Phe Gly Tyr Val 195 200 205 Gly Ala Phe Lys Cys Leu Lys Asp Gly Gly Gly Asp Val Ala Phe Val 210 215 220 Lys His Thr Thr Ile Phe Glu Val Leu Pro Glu Lys Ala Asp Arg Asp 225 230 235 240 Gln Tyr Glu Leu Leu Cys Leu Asp Asn Thr Arg Lys Pro Val Asp 245 250 <210> 694 <211> 255 <212> PRT <213> Mouse <400> 694 Gly Ala Pro Thr Pro Ala Tyr Val Arg Ser Ala Arg Arg Thr Glu Pro 10 15 Leu Ala Ser Gly Ala Arg Ser Arg Leu Cys Gln Cys Arg Arg Val Pro 20 25  $\cdot 30$ Ala Arg Lys Gln Gly Fro Gln Glu Gln Gly Gly Ser Gly Glu Ser Thr 35 40 45Thr Ser Ser Pro Gln Trp Trp Arg Arg Trp Arg Arg Leu Trp Ser Thr 50 60Cys Ser Cys Ser Ala Asp Asp Arg His Thr Gly Ser His Thr Asp Leu 65 70 75 80

Lys Glu Glu Thr Pro Ser Trp Thr Gln Ile Ser Val Val Phe Arg Lys

Asp Gly Gln Asp Glu Leu Gln Ala Ala His Lys Ala His Gly Ser Gly 100 105 110

85

```
Ser Pro Leu Thr Asn Gln Glu Ile Pro Ser Ser Ser Gly Ser Gly Phe
        115
                             120
                                                125
 Ile Val Ser Glu Asp Gly Leu Ile Val Thr Asn Ala His Val Leu Thr
    130
                         135
Asn Gln Gln Lys Ile Gln Val Glu Leu Gln Ser Gly Ala Arg Tyr Glu
145 150 155 160
Ala Thr Val Lys Asp Ile Asp His Lys Leu Asp Leu Ala Leu Ile Lys
165 170 175
Ile Glu Pro Asp Thr Glu Leu Pro Val Leu Leu Leu Gly Arg Ser Ser 180 195
Asp Leu Arg Ala Gly Glu Phe Val Val Ala Leu Gly Ser Pro Phe Ser
195 200 205
Leu Gln Asn Thr Val Thr Ala Gly Ile Val Ser Thr Thr Gln Arg Gly
210 215 220
Gly Arg Glu Leu Gly Leu Lys Asn Ser Asp Ile Asp Tyr Ile Gln Thr
                   230
                               235
Asp Ala Ile Ile Asn His Gly Asn Ser Gly Gly Pro Leu Val Asn
                245
                                     250
<210> 695
<211> 174
<212> PRT
<213> Mouse
<400> 695
Met Pro Ala Cys Arg Leu Cys Leu Leu Ala Ala Gly Leu Leu Gly
                                     10
Leu Leu Phe Thr Pro Ile Ser Ala Thr Gly Thr Asp Ala Glu Lys
            20
                                 25
Pro Gly Glu Cys Pro Gln Leu Glu Pro Ile Thr Asp Cys Val Leu Glu . 35 40 45
                            40
Cys Thr Leu Asp Lys Asp Cys Ala Asp Asn Arg Lys Cys Cys Gln Ala 50 60
Gly Cys Ser Ser Val Cys Ser Lys Pro Asn Gly Pro Ser Glu Gly Glu 65 70 75 80
Leu Ser Gly Thr Asp Thr Lys Leu Ser Glu Thr Gly Thr Thr Thr Gln
              85
                                   90
Ser Ala Gly Leu Asp His Thr Thr Lys Pro Pro Gly Gly Gln Val Ser 100 105 110
Thr Lys Pro Pro Ala Val Thr Arg Glu Gly Leu Gly Val Arg Glu Lys
115 120 125
Gln Gly Thr Cys Pro Ser Val Asp Ile Pro Lys Leu Gly Leu Cys Glu
   130
                       135
                                           140
Asp Gln Cys Gln Val Asp Ser Gln Cys Ser Gly Asn Met Lys Cys Cys
                   150
                                      155
Arg Asn Gly Cys Gly Lys Met Ala Cys Thr Thr Pro Lys Phe
               165
                                    170
<210> 696
<211> 193
<212> PRT
<213> Mouse
<400> 696
Leu Ala Thr Leu Val Gln Val Ser Arg Ile Arg Ala Tyr Ser Gln Gly
               5
                                    10
Gln Thr Gln Asp Gln Gln Gly Ser Ser Leu Asp Lys Val Ala Val
```

```
Pro Arg Glu Gln Thr His Ser Gly Leu Glu Gln Ile Gln Gln Ile Gln 35 40 45
 Gln Gln Leu Thr Gln Phe Asn Ala Ser Leu Ala Gly Leu Cys Arg Pro
                           55
Cys Pro Trp Asp Trp Glu Leu Phe Gln Gly Ser Cys Tyr Leu Phe Ser 65 70 75 80
Arg Thr Leu Gly Ser Trp Glu Thr Ser Ala Ser Ser Cys Glu Asp Leu
85 90 95
Gly Ala His Leu Val Ile Val Asn Ser Val Ser Glu Gln Arg Phe Met
100 105 110
Lys Tyr Trp Asn Val Arg Lys Asn Gln Arg Ser Trp Ile Gly Leu Ser
115 120 125
Asp His Ile His Glu Gly Ser Trp Gln Trp Val Asp Gly Ser Ala Leu
130 135 140
Lys Phe Ser Phe Trp Lys Glu Gly Glu Pro Asn Asn Asp Gly Asp Glu 145 150 155 160
Asp Cys Val Glu Leu Phe Met Asp Asp Trp Asn Asp Asn Lys Cys Thr
165 170 170
 Glu Gln Asn Phe Trp Val Cys Glu Gln Pro Ser Ala Pro Cys Pro His
                                      185
<210> 697
<211> 173
 <212> PRT
<213> Mouse
<400> 697
Val Arg Asn Gly Asp Leu Phe Phe Lys Lys Val Gln Val Glu Asp Gly 1 5 10 15
Gly Val Tyr Thr Cys Tyr Ala Met Gly Glu Thr Phe Asn Glu Thr Leu 20 25 30
Ser Val Glu Leu Lys Val Tyr Asn Phe Thr Leu His Gly His His Asp
35 40 45
Thr Leu Asn Thr Ala Tyr Thr Thr Leu Val Gly Cys Ile Leu Ser Val 50 55 60
Val Leu Val Leu Ile Tyr Leu Tyr Leu Thr Pro Cys Arg Cys Trp Cys 65 70 75 80
Arg Gly Val Glu Lys Pro Ser Ser His Gln Gly Asp Ser Leu Ser Ser 85 90 95
Ser Met Leu Ser Thr Thr Pro Asn His Asp Pro Met Ala Gly Gly Asp 100 105 110
Lys Asp Asp Gly Phe Asp Arg Val Ala Phe Leu Glu Pro Ala Gly 115 120 125
Pro Gly Gln Gly Gln Asn Gly Lys Leu Lys Pro Gly Asn Thr Leu Pro
130 135 140

Val Pro Glu Ala Thr Gly Lys Gly Gln Arg Arg Met Ser Asp Pro Glu
145 150 155 160
Ser Val Ser Ser Val-Phe Ser Asp Thr Pro Ile Val Val
                  165
                                         170
<210> 698
<211> 88
<212> PRT
```

<213> Mouse

<400> 698

```
Met Glu Glu Ile Thr Cys Ala Phe Leu Leu Leu Leu Ala Gly Leu Pro
1 5 10 15
Ala Leu Glu Ala Ser Asp Pro Val Asp Lys Asp Ser Pro Phe Tyr Tyr
            20
                                25
Asp Trp Glu Ser Leu Gln Leu Gly Gly Leu Ile Phe Gly Gly Leu Leu 35 40 45
Cys Ile Ala Gly Ile Ala Met Ala beu Ser Gly Lys Cys Lys Cys Arg
                       55
                                            60
Arg Thr His Lys Pro Ser Ser Leu Pro Gly Lys Ala Thr Pro Leu Ile 65 70 75 80
Ile Pro Gly Ser Ala Asn Thr Cys
                 85
<210> 699
<211> 155
<212> PRT
<213> Mouse
Met Tyr Ser Glu Gly Ala Pro Phe Trp Thr Gly Ile Val Ala Met Leu
 1
                                    10
Ala Gly Ala Val Ala Phe Leu His Lys Lys Arg Gly Gly Thr Cys Trp 20 25 30
Ala Leu Met Arg Thr Leu Leu Val Leu Ala Ser Phe Cys Thr Ala Val
       35
                            40
Ala Ala Ile Val Ile Gly Ser Arg Glu Leu Asn Tyr Tyr Trp Tyr Phe 50 . . 55 60
Leu Gly Asp Asp Val Cys Gln Arg Asp Ser Ser Tyr Gly Trp Ser Thr
                    -70
Met Pro Arg Thr Thr Pro Val Pro Glu Glu Ala Asp Arg Ile Ala Leu
                85
                                    90
Cys Ile Tyr Tyr Thr Ser Met Leu Lys Thr Leu Leu Met Ser Leu Gln
                                105
           100
                                                   110
Ala Met Leu Leu Gly Ile Trp Val Leu Leu Leu Leu Ala Ser Leu Thr
115 120 125
                                               125
Pro Val Cys Val Tyr Ile Trp Lys Arg Phe Phe Thr Lys Ala Glu Thr
  130
                      135
Glu Glu Lys Lys Leu Leu Gly Ala Ala Val Ile
145
                    150
<210> 700
<211> 255
<212> PRT
<213> Mouse
<400> 700
Met Leu Gln His Thr Ser Leu Val Leu Leu Leu Ala Ser Ile Trp Thr
                                    10
Thr Arg His Pro Val Gln Gly Ala Asp Leu Val Gln Asp Leu Ser Ile
            20
                                25
Ser Thr Cys Arg Ile Met Gly Val Ala Leu Val Gly Arg Asn Lys Asn 35 40 45
                            40
                                                45
Pro Gln Met Asn Phe Thr Glu Ala Asn Glu Ala Cys Lys Met Leu Gly
```

55

Leu Thr Leu Ala Ser Arg Asp Gln Val Glu Ser Ala Gln Lys Ser Gly

Phe Glu Thr Cys Ser Tyr Gly Trp Val Gly Glu Gln Phe Ser Val Ile

. 90

85

```
Pro Arg Ile Phe Ser Asn Pro Arg Cys Gly Lys Asn Gly Lys Gly Val
  Leu Ile Trp Asn Ala Pro Ser Ser Gln Lys Phe Lys Ala Tyr Cys His
115
120
125

Asn Ser Ser Asp Thr Trp Val Asn Ser Cys Ile Pro Glu Ile Val Thr
130
135
140
  Thr Phe Tyr Pro Val Leu Asp Thr Gln Thr Pro Ala Thr Glu Phe Ser 145 150 155 160
  Val Ser Ser Ser Ala Tyr Leu Ala Ser Ser Pro Asp Ser Thr Thr Pro
165 170 175
                                                               175
   Val Ser Ala Thr Thr Arg Ala Pro Pro Leu Thr Ser Met Ala Arg Lys
180 185 190
   Thr Lys Lys Ile Cys Ile Thr Glu Val Tyr Thr Glu Pro Ile Thr Met 195 200 205
  Ala Thr Glu Thr Glu Ala Phe Val Ala Ser Gly Ala Ala Phe Lys Asn
210 215 220
  Glu Ala Ala Gly Phe Gly Gly Val Pro Thr Ala Leu Leu Val Leu Ala
225 230 235 240
                                   235 240
  Leu Leu Phe Phe Gly Ala Ala Ala Val Leu Ala Val Cys Tyr Val
                                        250
<210> 701
  <211> 91
  <212> PRT
   <213> Mouse
  Met Val Trp Ala Asn Leu Ala Val Phe Val Ile Cys Phe Leu Pro Leu
  His Val Val Leu Thr Val Gln Val Ser Leu Asn Leu Asn Thr Cys Ala
20 25 30
  Ala Arg Asp Thr Phe Ser Arg Ala Leu Ser Ile Thr Gly Lys Leu Ser
35 40 45
                                                      45
  Asp Thr Asn Cys Cys Leu Asp Ala Ile Cys Tyr Tyr Tyr Met Ala Arg . 50 55 60
                          55
  Glu Phe Gln Glu Ala Ser Lys Pro Ala Thr Ser Ser Asn Thr Pro His
                      70
                                            75
  Lys Ser Gln Asp Ser Gln Ile Leu Ser Leu Thr
                   85
  <210> 702
  <211> 244
  <212> PRT
  <213> Mouse
  <400> 702
  Gly Trp Gln Gly Ala Pro Asp Pro Arg Gly Leu Gly Gln Leu Ser Gln
                                          10
  Pro Tyr Met Gly Glu Met Pro Trp Thr Ile Leu Leu Phe Ala Ser 20 25 30
  Gly Ser Leu Ala Ile Pro Ala Pro Ser Ile Ser Leu Val Pro Pro Tyr 35 40 45
  Pro Ser Ser His Glu Asp Pro Ile Tyr Ile Ser Cys Thr Ala Pro Gly
```

 Asp
 Ile
 Leu
 Gly
 Ala
 Asn
 Phe
 Thr
 Leu
 Phe
 Arg
 Gly
 Gly
 Glu
 Val
 Val
 Asp
 Fre
 Fre
 Fre
 Fre
 Fre
 Fre
 Boy
 Fre
 Fre
 Boy
 th

<210> 703 <211> 255 <212> PRT <213> Mouse

<400> 703

Met Ala Gln Leu Ala Arg Ala Thr Arg Ser Pro Leu Ser Trp Leu Leu 10 Leu Leu Phe Cys Tyr Ala Leu Arg Lys Ala Gly Gly Asp Ile Arg Val 20 25 30 Leu Val Pro Tyr Asn Ser Thr Gly Val Leu Gly Gly Ser Thr Thr Leu 35 His Cys Ser Leu Thr Ser Asn Glu Asn Val Thr Ile Thr Gln Ile Thr 50 55 60 Trp Met Lys Lys Asp Ser Gly Gly Ser His Ala Leu Val Ala Val Phe 65 70 75 80 His Pro Lys Lys Gly Pro Asn Ile Lys Glu Pro Glu Arg Val Lys Phe 85 90 95 Leu Ala Ala Gln Gln Asp Leu Arg Asn Ala Ser Leu Ala Ile Ser Asn 100 105 110 Leu Ser Val Glu Asp Glu Gly Ile Tyr Glu Cys Gln Ile Ala Thr Phe
115 120 125. Pro Arg Gly Ser Arg Ser Thr Asn Ala Trp Leu Lys Val Gln Ala Arg 130 135 140 Pro Lys Asn Thr Ala Glu Ala Leu Glu Pro Ser Pro Thr Leu Ile Leu 145 150 155 160 Gln Asp Val Ala Lys Cys Ile Ser Ala Asn Gly His Pro Pro Gly Arg 165 170 175 Ile Ser Trp Pro Ser Asn Val Asn Gly Ser His Arg Glu Met Lys Glu 180 185 190 Pro Gly Ser Gln Pro Gly Thr Thr Thr Val Thr Ser Tyr Leu Ser Met 200 205

```
Val Pro Ser Arg Gln Ala Asp Gly Lys Asn Ile Thr Cys Thr Val Glu
    210
                        215
                                               220
His Glu Ser Leu Gln Glu Leu Asp Gln Leu Leu Val Thr Leu Ser Gln 225 230 235 240
Pro Tyr Pro Pro Glu Asn Val Ser Ile Ser Gly Tyr Asp Gly Asn
                 245
                                       250
<210> 704
<211> 255
<212> PRT
<213> Mouse
<400> 704
Met Phe Leu Val Gly Ser Leu Val Val Leu Cys Gly Leu Leu Ala His
1 5 10 15
Ser Thr Ala Gln Leu Ala Gly Leu Pro Leu Pro Leu Gly Gln Gly Pro
20 25 30
Pro Leu Pro Leu Asn Gln Gly Pro Pro Leu Pro Leu Asn Gln Gly Gln
       35
                             40
                                                  45
Leu Leu Pro Leu Ala Gln Gly Leu Pro Leu Ala Val Ser Pro Ala Leu 50 55 60
Pro Ser Asn Pro Thr Asp Leu Leu Ala Gly Lys Phe Thr Asp Ala Leu 65 70 75 80
                                          75 .
Ser Gly Gly Leu Leu Ser Gly Gly Leu Leu Gly Ile Leu Glu Asn Ile 85 90 95
Pro Leu Leu Asp Val Ile Lys Ser Gly Gly Gly Asn Ser Asn Gly Leu 100 105 110
Val Gly Gly Leu Leu Gly Lys Leu Thr Ser Ser Val Pro Leu Leu Asn 115 120 125
Asn Ile Leu Asp Ile Lys Ile Thr Asp Pro Gln Leu Leu Glu Leu Gly 130 135 140
Leu Val Gln Ser Pro Asp Gly His Arg Leu Tyr Val Thr Ile Pro Leu
145 150 155 160
Gly Leu Thr Leu Asn Val Asn Met Pro Val Val Gly Ser Leu Leu Gln
165 170 175
                                    170 175
Leu Ala Val Lys Leu Asn Ile Thr Ala Glu Val Leu Ala Val Lys Asp
180 185 190
Asn Gln Gly Arg Ile His Leu Val Leu Gly Asp Cys Thr His Ser Pro
195 200 205
Gly Ser Leu Lys Ile Ser Leu Leu Asn Gly Val Thr Pro Val Gln Ser
210 215 220
Phe Leu Asp Asn Leu Thr Gly Ile Leu Thr Lys Val Leu Pro Glu Leu
225 230 235 240
Ile Gln Gly Lys Val Cys Pro Leu Val Asn Gly Ile Leu Ser Gly
                245
                                      250
                                                            255
<210> 705
<211> 255
<212> PRT
<213> Mouse
Met Ala Thr Thr Cys Gln Val Val Gly Leu Leu Leu Ser Leu Leu
                 5
                                     10
Gly Leu Ala Gly Cys Ile Ala Ala Thr Gly Met Asp Met Trp Ser Thr
           20
                                 25
                                                    . 30
Gln Asp Leu Tyr Asp Asn Pro Val Thr Ala Val Phe Gln His Glu Gly
```

```
40
Leu Trp Arg Ser Cys Val Gln Gln Ser Ser Gly Phe Thr Glu Cys Arg
                        55
                                              60
Pro Tyr Phe Thr Ile Leu Gly Leu Pro Ala Met Leu Gln Ala Val Arg
                   70
                                         75
Ala Leu Met Ile Val Gly Ile Val Leu Gly Val Ile Gly Ile Leu Val
85 90 95
Ser Ile Phe Ala Leu Lys Cys'Ile Arg Ile Gly Ser Met Asp Asp Ser
100 105 110
Ala Lys Ala Lys Met Thr Leu Thr Ser Gly Ile Leu Phe Ile Ile Ser
115 120 125
                                                125
Gly Ile Cys Ala Ile Ile Gly Val Ser Val Phe Ala Asn Met Leu Val
130 135 140
                                     140
Thr Asn Phe Trp Met Ser Thr Ala Asn Met Tyr Ser Gly Met Gly Gly 145 150 155 160
Met Gly Gly Met Val Gln Thr Val Gln Thr Arg Tyr Thr Phe Gly Ala
165 170 175
Ala Leu Phe Val Gly Trp Val Ala Gly Gly Leu Thr Leu Ile Gly Gly 180 185 190
Val Met Met Cys Ile Ala Cys Arg Gly Leu Thr Pro Asp Asp Ser Asn
195 200 205
Phe Lys Ala Val Ser Tyr His Ala Ser Gly Gln Asn Val Ala Tyr Arg
   210
                        215
                                         220
Pro Gly Gly Phe Lys Ala Ser Thr Gly Phe Gly Ser Asn Thr Arg Asn 225
                   230
                                       235
Lys Lys Ile Tyr Asp Gly Gly Ala Arg Thr Glu Asp Asp Glu Gln
                245
                                      250
<210> 706
```

<211> 255 <212> PRT <213> Mouse

Met Gly Arg Phe Ala Ala Ala Leu Val Gly Ser Leu Phe Trp Leu Gly 10 Leu Leu Leu Cys Gly Leu Gly Ser Leu Ala Ser Ala Glu Pro Arg Ala
. 20 25 30 Pro Pro Asn Arg Ile Ala Ile Val Gly Ala Gly Ile Gly Gly Thr Ser 35 40 Ser Ala Tyr Tyr Leu Arg Lys Lys Phe Gly Lys Asp Val Lys Ile Asp 50 55 60 Val Phe Glu Arg Glu Glu Val Gly Gly Arg Leu Ala Thr Leu Lys Val 65 70 . 75 80 Gln Gly His Asp Tyr Glu Ala Gly Gly Ser Val Ile His Pro Leu Asn 85 90 95 Leu His Met Lys Arg Phe Val Lys Glu Leu Gly Leu Ser Ser Val Pro 100 105 110 Ala Ser Gly Gly Leu Val Gly Val Tyr Asn Gly Lys Ser Leu Val Phe 115 120 125 Glu Glu Ser Ser Trp Phe Val Ile Asn Val Ile Lys Leu Val Trp Arg 130 135 140 135 140 Tyr Gly Phe Gln Ser Leu Arg Met His Met Trp Val Glu Asp Leu Leu 145 150 155 160 Asp Lys Phe Met Arg Ile Tyr Arg Tyr Gln Ser His Asp Tyr Ala Phe 165 170 175 Ser Ser Val Glu Lys Leu Met His Ala Ile Gly Gly Asp Asp Tyr Val

```
185
Arg Leu Leu Asn Gln Thr Leu Arg Glu Asn Leu Lys Lys Ala Gly Phe
       195
                          200
                                                  205
Ser Glu Thr Phe Leu Asn Glu Met Ile Ala Pro Val Met Lys Val Asn
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Gln Asp Gly Arg Asp Glu Glu Lys Met Tyr Glu Asn Val Leu Asn Ser 50 60
Ser Pro Gly Gln Leu Pro Ala Leu Pro Pro Arg Gly Ser Pro Phe Pro 65 70 75 80
Gly Asp Leu Ala Pro Gln Glu Ala Pro Arg Gln Pro Ser Ala Trp Tyr
85 90 95
Ser Ser Val Lys Lys Val Arg Asn Lys Lys Val Phe Ala Ile Ser Gly 100 105 110
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His Val Pro Gly Gly His Ala Pro Gly Pro Ser His Lys Trp Leu Cys 50 60
Thr Ala Ala Leu Trp Arg Tyr Leu Glu His Ser Ala Val Thr His Gly 65 70 75 80
Thr Ala Leu Pro Glu Ala His Ala Val Arg Gly Lys His Gly Lys Lys
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Val Thr Pro Asn Tyr Leu Asp Asn Val Ser Ala Arg Val Ala Pro Trp 50 55 60
Cys Gly Cys Ala Ala Ser Gly Asn Arg Arg Glu Glu Cys Glu Ala Phe
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Arg Lys Leu Phe Thr Arg Asn Pro Cys Leu Asp Gly Ala Ile Gln Ala
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Lys Glu Ile Phe Leu Arg Glu Leu Ile Ser Asn Ala Ser Asp Ala Leu 100 105 110
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Asp Lys Ile Arg Leu Ile Ser Leu Thr Asp Glu Asn Ala Leu Ala Gly
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Asn Glu Glu Leu Thr Val Lys Ile Lys Cys Asp Lys Glu Lys Asn Leu
130 135 140
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Lys Asn Leu Gly Thr Ile Ala Lys Ser Gly Thr Ser Glu Phe Leu Asn
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Lys Met Thr Glu Ala Gln Glu Asp Gly Gln Ser Thr Ser Glu Leu Ile
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Val Ile Val Thr Ser Lys His Asn Asp Thr Gln His Ile Trp Glu
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His Glu His Phe Lys Gly Arg Leu Ile Leu Asn Trp Thr Gln Gly Gln 100 105 110
Thr Ser Gly Val Leu Arg Ile Leu Asn Leu Lys Glu Ser Asp Gln Ala 115 120 125
Gln Tyr Phe Ser Arg Val Asn Leu Gln Ser Thr Glu Gly Met Lys Leu
130 135 140
Trp Gln Ser Ile Pro Gly Thr Gln Leu Asn Val Thr Gln Ala Leu Asn 145 150 155 160
Thr Thr Met Arg Ser Pro Phe Ile Val Thr Ser Glu Phe Thr Thr Ala
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Gly Leu Glu His Thr Ser Asp Gln Arg Asn Pro Ser Leu Met Asn Leu
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Thr Cys Pro Leu Pro Glu Leu Gln Asn Ile Leu Ile Cys Ser Phe Ser
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Gln Val Val Lys Ile Leu Val Val Thr Val Gln Leu Ile Leu Phe Gly 35 . 40 45
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Phe Ala Ala Tyr Thr Gin Glu Gln Leu Tyr Gin Ala Ile Phe Tyr Ala 85 90 95 .
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100 105 110
Tyr Val Arg Gly Gly Gly Gly Pro Trp Ala Asn Gly Ser Ala Leu Ala
115 120 125
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180 185 190
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Leu Ile Asn Asn Glu Ile Pro Asp Cys Tyr Thr Phe Ser Ile Leu Ile 210 215 220 .
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65 70 75 80
Arg His Ile Tyr Arg Asp Leu Glu Ala Ala Asp Ala Ala Leu Gln
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Ala Gly Lys Gly Glu Glu Glu Ile Leu Pro Pro Cys Asn Leu Gln Val
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Ala Glu Arg Val Arg Lys Glu Val Gly Glu Val Ser Val Leu Val Asn
130 135 140
Asn Ala Gly Val Gly Ser Gly His His Leu Leu Glu Cys Pro Asp Glu
145 150 155 160
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165 170 175
                                      170
Thr Lys Ala Phe Leu Pro Thr Met Leu Glu Ile Asn His Gly His Ile
180 185 190
Val Thr Val Ala Ser Ser Leu Gly Leu Phe Ser Thr Ala Gly Val Glu
195 200 205
Asp Tyr Cys Ala Ser Lys Phe Gly Val Val Gly Phe His Glu Ser Leu
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Arg Tyr Phe Leu Ile Tyr Leu Leu Thr Leu Thr Ala Ser Ala Ala Thr 50 55 60
Ile Ala Thr Val Thr Ala Ala Phe Leu Leu Arg Leu Val Thr Val Ser 65 70 75 80
Asp Leu Tyr Glu Glu Thr Tyr Leu Asp Asp Val Gly His Phe Gln Ala 85 90 95
Val Asp Thr Val Phe Leu Ile Gln His Leu Phe Leu Ala Phe Pro Arg
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Pro Ser Tyr Lys Lys Lys Glu'Lys
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Ser Ile Ile Leu Thr Arg Ala Ser Ser Cys Ser Leu Ser Leu Ser Leu 85 90 95
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Thr Asp Thr Ser Ser His Glu Ala Ala Thr Lys Ala Val Leu Gln Glu 115 120 125
Phe Gly Lys Ile Asp Ile Leu Val Asn Asn Gly Gly Arg Ser Gln Arg 130 135 140 . . .
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Leu Asn Tyr Ile Gly Thr Val Ser Leu Thr Lys Cys Val Leu Pro His
165 170 175
Met Ile Glu Arg Lys Gln Gly Lys Ile Val Thr Val Asn Ser Ile Ala
180 185 190
Gly Ile Ala Ser Val Ser Leu Ser Ser Gly Tyr Cys Ala Ser Lys His
195 200 205
Ala Leu Arg Gly Phe Phe Asn Ala Leu His Ser Glu Leu Gly Gln Tyr 210 215 220
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Ser Thr Ser Phe Phe Ile Ala Leu Val Val Phe Tyr Ile Leu Phe Cys
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Gln Gln Ser Gly Gly Trp Gly Ser Pro Arg Lys Asp Ser Val Leu Lys
165 170 175
Arg Gly Ile Arg Ala Ala Gly Ala Gly Ala Ser Ala Pro Ser Thr Gln
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Ser Arg Asn Leu Ser Ala Ser Ser Pro Gln Leu Leu Leu Pro Pro Lys 50 60 .
Cys Glu Met Leu His Val Ala Ile Val Cys Ala Gly Tyr Asn Ser Ser 65 70 75 80
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Glu Thr Leu Phe Arg Thr Trp Met Val Pro Ala Val Val Ser Phe 115 120 125
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Asp Lys Gln Val Val Gly Leu Val Glu Asn Gln Ser Asp Trp Tyr Leu 195 200 205
Gly Asn Leu Trp Lys Asn His Arg Pro Trp Pro Ala Leu Gly Arg Gly 210 215 220
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Phe Asn Thr Gly Val Ile Leu Leu Trp Leu Asp Arg Leu Gln Gln Thr
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International application No.

PCT/NZ01/00099

Α.	CLASSIFICATION OF SUBJECT MATTER					
Int. Cl. 7:	C12N 15/12, 15/18, 15/19					
According to	International Patent Classification (IPC) or to both	national classification and IPC				
В.						
	Minimum documentation searched (classification system followed by classification symbols)					
AS BELOW						
AS BELOW	searched other than minimum documentation to the ex	tent that such documents are included in th	e fields searched			
•	Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)					
Dgene, Swis	s Prot, EMBL, Genebank, : SEQ ID. NOS. 1	- 10.				
c.	DOCUMENTS CONSIDERED TO BE RELEVANT	г				
Category*	Citation of document, with indication, where app	propriate, of the relevant passages	Relevant to claim No.			
P, X	EP 1 067 182 HELIX RESEARCH INSTITUTE (10 January 2001) See Sequence Id. 487, & GeneBank Accession Number AX136565.		1 - 3. (SEQ ID NO 1)			
P, X	EP 1067 182 HELIX RESEARCH INSTITUTE (10 January 2001) See Sequence Id. 219, & GeneBank Accession NumberAX136297.		1 - 3. (SEQ ID NO 1)			
х	X EMBL Accession Number AC008119 (9 October 1999) Homo sapiens 12q24.1-116.6-118.9 BAC RPCI11-951II1		1 - 3. (SEQ ID NO 1)			
<b>X</b>	Further documents are listed in the continuati	on of Box C X See patent fam	nily annex			
* Special categories of cited documents:  "A" document defining the general state of the art which is not considered to be of particular relevance  "E" earlier application or patent but published on or after the international filing date  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) document referring to an oral disclosure, use, exhibition or other means  "P" document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention document of particular relevance; the claimed invention cannot be considered novel or cannot be considered novel or cannot be considered novel or cannot be considered to involve an inventive step when the document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document of particular relevance; the claimed invention cannot be considered novel or cannot be considered novel or cannot be considered novel or cannot be considered novel or cannot be considered novel or cannot be considered novel or cannot be considered novel or cannot be considered novel or cannot be considered novel or cannot be considered novel or cannot be						
Date of the actual completion of the international search  20 August 2001  Date of mailing of the international search report  21 Separational search report						
Name and mail: AUSTRALIAN PO BOX 200, V	ing address of the ISA/AU I PATENT OFFICE WODEN ACT 2606, AUSTRALIA pct@ipaustralia.gov.au	ALISTAIR BESTOW Telephone No: (02) 6283 2450	; ·			

International application No. PCT/NZ01/00099

		PCT/NZ01/0009	77		
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT					
Category*	Citation of document, with indication, where appropriate, of the relevant pas	sages Rele	evant to claim No.		
х	US, A, 5 952 486 L. N. BLOKSBERG ET. AL. (14 September 1999) ID 53. & GeneBank Accession number AR074144.	See SEQ 1 - 3	3. (SEQ ID NO 2)		
х	WO, A, 2000 40752 THE NOTTINGHAM TRENT UNIVERSITY (2000) See SEQ ID NO. 2. & GeneBank Accession Number AX02654		3. (SEQ ID NO 2)		
x	EMBL Accession Number UCAJ4935 (2 March 1999.) Urechis caup for cytoplasmic intermediate filament protein.	o mRNA 1 - 3	3. (SEQ ID NO 2)		
x	WO, A, 99 53040 MËTAGEN GESELLSCHAFT FÜR GENOMFORSCHUNG MBH (21 October 1999) See SEQ ID 31. & Accession Number AX014842.	GenBank	3. (SEQ ID NO 4)		
P, X	WO, A, 2001 07612 INCYTE GENOMICS, INC. (1 February 2001) ID 43 & Genebank Accession Number AX078375.	See SEQ 1 - 3	3. (SEQ ID NO 4)		
P, X	WO, A, 2001 10902 CURAGEN CORPORATION (15 February 200 SEQ ID 5 & Genebank Accession Number AX084211.	1) See   1 - 3	3. (SEQ ID NO 5)		
x	EMBL Accession Number AF169677 (29 JANUARY 2000) Homo sileucine-rich repeat transmembrane protein FLRT3 (FLRT3) mRNA, cds.		3. (SEQ ID NO 5)		
x	EMBL Accession Number RNMOG (20 August 1992) Rattus norveg myelin/oligodendrocyte glycoprotein (MOG) gene, complete cds.	icus 1 - 3	3. (SEQ ID NO 7)		
A	EMBL Accession Number D50030 (14 April 2000) Homo sapiens ge hepatocyte growth factor activator, complete cds.	ne for 1 - 3	. (SEQ ID NO 8)		
х	WO, A, 99 55865 GENESIS RESEARCH AND DEVELOPMENT CORPORATION LIMITED (4 November 1999) See SEQ ID NOS 1 187, 196, 294, 295 and 395.	- 10, 147, (SE	- 3, 8-17, 27-29 Q ID NOS 1-10, 7, 196, 294, 295, 413-5, 417)		
P, X	WO, A, 2000 69884 GENESIS RESEARCH AND DEVELOPMENT CORPORATION LIMITED (23 November 2000) See SEQ ID NOS 147, 187, 196, 294, 295 and 395.	I - 10, (SE	- 3, 8-17, 27-29 Q ID NOS 1-10, 7, 196, 294, 295, 413-5, 417)		

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C (Continua	tion) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	WO, A, 00 63230 HUMAN GENOME SCIENCES, INC. (26 October 2000) See SEQ ID NO 68 and pages 16-29	1-3, 8-17, 27 29 (SEQ ID NOS 196, 413-5, 417
x	WO, A, 00 29438 MILLENNIUM PHARMACEUTICALS, INC. (25 May 2000) See Figures 1, 3, 5,7 and 8	1-3, 8-17, 27 29 (SEQ ID NOS 196, 413-5, 417
PX	WO, A, 00 63377 ZYMOGENETICS, INC. (26 October 2000) See SEQ ID NOS 1 and 11	1-3 (SEQ ID NO 147, 294
PX	WO, A, 01 49728 PROTOGENE, INC. (12 July 2001) See SEQ ID NO 59 and Table 1	1-3 (SEQ ID NO 147)
PX	WO, A, 00 73448 ZYMOGENETICS, INC. (7 December 2000) See SEQ ID NOS 1 and 14	1-3 (SEQ ID NO 294)
x	GenPept Accession No. CAB53702 (18 February 2000) Hypothetical Protein Homo sapiens Ottenwaelder B et al	1-3 (SEQ ID NO 295)
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PCT/NZ01/00099 Box I Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet) This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons: Claims Nos: 1. because they relate to subject matter not required to be searched by this Authority, namely: 2. Claims Nos: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically: 3. Claims Nos: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)Box II Observations where unity of invention is lacking (Continuation of item 3 of first sheet) This International Searching Authority found multiple inventions in this international application, as follows: As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims 2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee. 3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: 1-3, 8-17 and 27-29 (SEQ ID NOS 1-10, 147, 196, 294, 295, 413-415, 417) More than one invention has been claimed. (continued in supplemental box 4. No required additional search fees were timely paid by the applicant. The additional search fees were accompanied by the applicant's protest. Remark on Protest No protest accompanied the payment of additional search fees.

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Supplemental Box

(To be used when the space in any of Boxes I to VIII is not sufficient)

#### Continuation of Box No: II

Rule 13.1 of the PCT states the principle that an International Application should relate to only one invention or, if there is more than one invention, that the inclusion of those inventions in one International Application is only permitted if all inventions are so linked to form a single general inventive concept. Rule 13.2 of the PCT defines the method for determining whether the requirement of unity of invention is satisfied in respect of a group of inventions claimed in the International application. Unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding "special technical features." The expression "special technical features" is defined in Rule 13.2 as meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art. The determination is made on the contents of the claims as interpreted in the light of the description and drawings (if any).

There is no special technical feature which is common to all 725 sequences disclosed in the specification. It is well known in the art that for a given cell type, the cell will express a great many sequences, each having a different function from the others. That they are sourced from skin cells is not a special technical feature. For applications claiming nucleotides and peptides, there are two features which are to be considered for the purposes of determining the number of inventions in a specification.

1) If the polynucleotide has a corresponding peptide, then the two sequences may have a common special technical feature because the nucleotide encodes the peptide. Therefore they are regarded as a single invention.

In the present case, the specification does not disclose a complete concordance between the polynucleotides and corresponding polypeptides, other than those disclosed in Table 2. While Table 2 purports to provide a concordance between nucleotides and peptides for which they code, this is incomplete, as the majority of sequences are not referred to on this table. Therefore the ISA is unable to confidently determine the number of inventions, on the basis of a concordance between the polynucleotides and the peptides.

2) A group of two or more nucleotides, or two or more peptides, which share a significant structural element. A "significant structural element" is the structural element that defines the specific biological activity of an amino acid sequence or a nucleotide sequence or its encoded polypeptide <u>and</u> is disclosed as the feature that defines the contribution which each of the inventions, considered as a whole, makes over the prior art. If each of the inventions shares the same significant structural element, then it provides the special technical feature which is required to establish unity of invention.

In the present case, genes and their expressed proteins from skin cells have been sequenced. The applicant has provided no evidence that the nucleotide sequences of the present application, and the peptides they express, all form a group of protein types sharing a significant structural element. On the contrary, the putative peptides derived from the nucleotide sequences of the application have a wide range of functions based on their similarity to known proteins. (see Table 2) At best, it appears from Table 2 that there may be 76 distinct protein types which share a common function, and therefore may share a common significant structural element. However, most of the polynucleotides and peptides which do not appear on Table 2, have not have been identified in terms of their function, much less, whether any of them have a shared significant structural element. Therefore, the ISA is unable to confidently determine the number of inventions, on the basis of a shared significant structural element. Thus, at this stage, in the absence of a complete polynucleotide peptide concordance, or the definition of a special technical feature which is common to two or more sequences, this ISA considers that that there are 72 groupings of sequences, which encompass the 725 sequences.

While the ISA is unable to determine the precise number of inventions in this application it is prepared, as a service, to search a first group of ten sequences for a single search fee. This offer is provided purely as a service to the applicant and should not be taken as having any bearing on the ISA's assessment of the number of inventions claimed in these 10 sequences. The ISA also agrees to search the two further inventions specified by the applicant in their letter of 30 August 2001, for two additional search fees. As such, the ISA has searched SEQ ID NOS 1-10, 147, 196, 294, 295, 413-5 and 417.